Forum Risk Management
obiettivo sanità salute
21-24 NOVEMBRE 2023
AREZZO FIERE E CONGRESSI
18

Nuove frontiere nel trattamento: Identificazione precoce e stratificazione del rischio di progressione

Disturbi del sonno e decadimento cognitivo

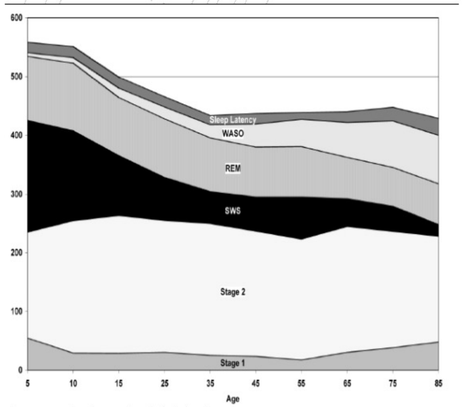
E. Bonanni

Centro di Riferimento Regionale Disturbi del Sonno

Azienda Ospedaliro Universitataria PISA

Meta-Analysis of Quantitative Sleep Parameters From Childhood to Old Age in Healthy Individuals: Developing Normative Sleep Values Across the Human Lifespan

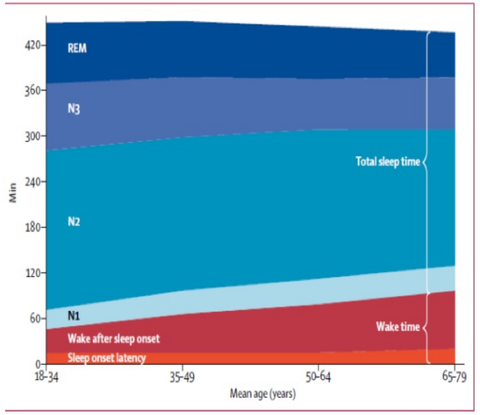
Maurice M. Ohayon, MD, DSc, PhD[1], Mary A. Carskadon, PhD[2], Christian Guilleminault, MD[3], Michael V. Vitiello, PhD[4]

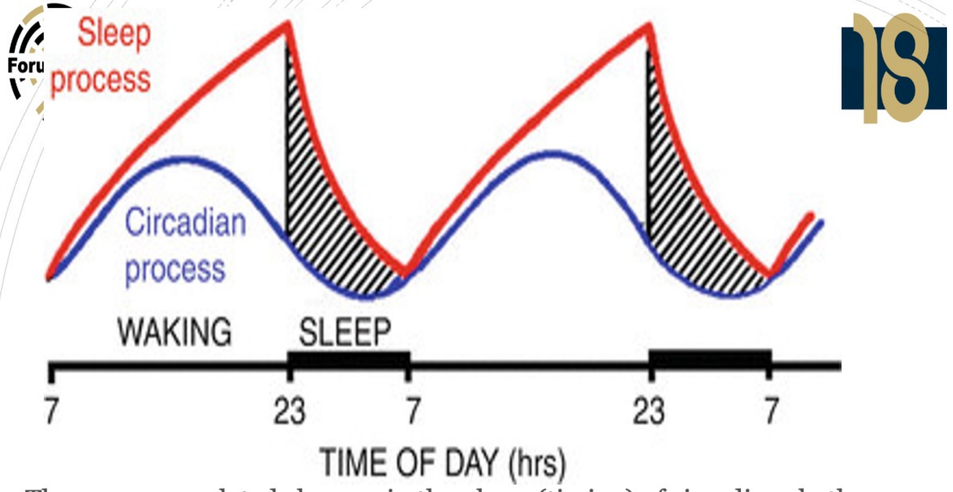


Normal polysomnography parameters in healthy adults: a systematic review and meta-analysis

Mark F Boulos*, Trevor Jairam*, Tetyana Kendzerska*, James Im, Anastasia Mekhael, Brian J Murray

Lancet Respir Med 2019





- There are age-related changes in the phase (timing) of circadian rhythms
- There are age-related changes in the amplitude of circadian rhythms
- There are age-related changes in how the circadian and sleep homeostatic systems interact
- With advancing age, the ability to sleep at adverse circadian phases is compromised, even in healthy individuals

Aging Brain 3 (2023) 100068
Contents lists available at ScienceDirect
Aging Brain
journal homepage: www.elsevier.com/locate/nbas

To sleep or not to sleep – Effects on memory in normal aging and disease

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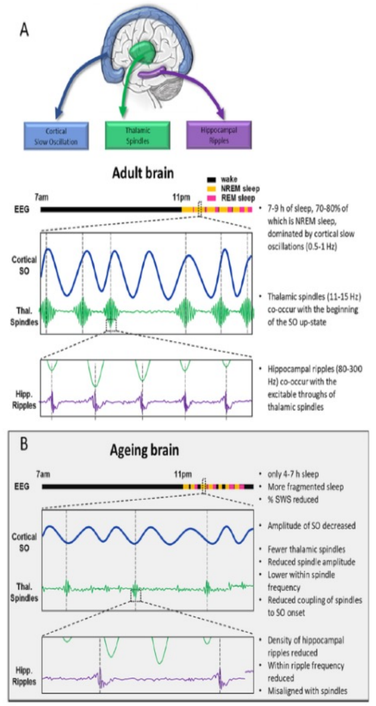

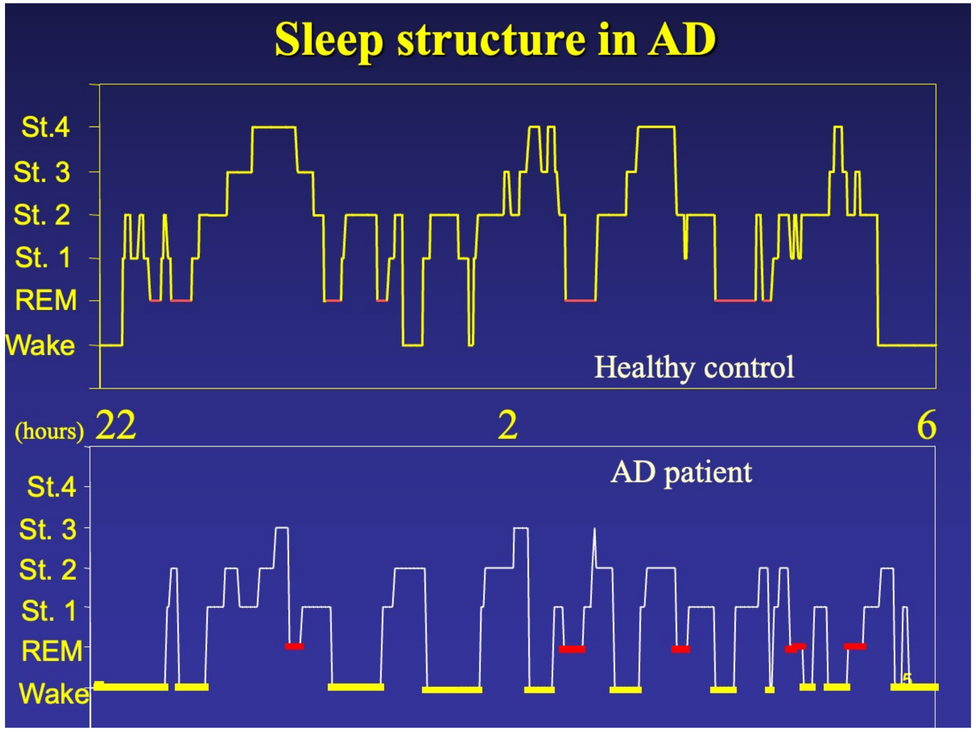

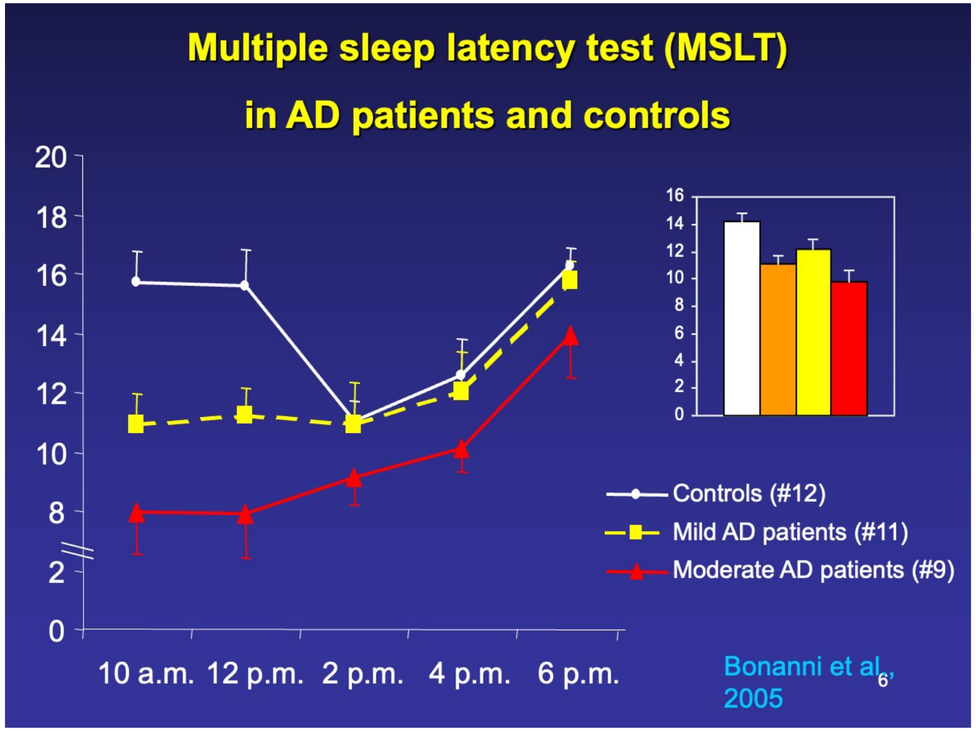

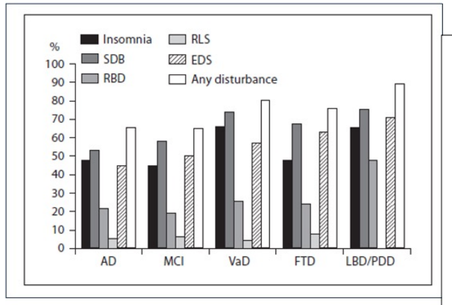

An important finding was that different sleep disturbances occurred almost invariably in association in the same patient confirming the need to deeply investigate each kind of sleep disturbance to reach correct therapies , avoiding interferences among treatments for different sleep disturbances.

Score for depressive symptoms more severe in persons with any sleep disorders

Table 1. Age and gender characteristics by sleep disturbance

	Women n (%)	Age years	Total
SDB			
Yes	130 (50.8)*	76.0 ± 8.4	255 [60.0]
No	111 (63.4)	75.9 ± 9.8	
EDS			
Yes	106 (49.8)*	76.4 ± 8.7	213 [50.1]
No	132 (62.6)	75.6 ± 9.3	
Insomnia			
Yes	119 (56.1)	77.0 ± 6.9*	212 [49.9]
No	120 (56.3)	74.8 ± 10.6	
RBD			
Yes	44 (45.8)*	75.2 ± 7.4	96 [22.6]
No	193 (59.0)	76.2 ± 9.4	
RLS			
Yes	16 (61.5)*	74.9 ± 8.1	26 [6.1]
No	223 (55.9)	76.0 ± 9.1	

SDB = Sleep-disordered breathing; RBD = REM behavior disorder; RLS = restless legs syndrome; EDS = excessive daytime sleepiness. Numbers in round parentheses are row percentages. Numbers in squared parentheses are column percentages, and ± are standard deviations.

* $p < 0.05$.

Recommendations of the Sleep Study Group of the Italian Dementia Research Association (SINDem) on clinical assessment and management of sleep disorders in individuals with mild cognitive impairment and dementia: a clinical review

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Il disturbo da insonnia

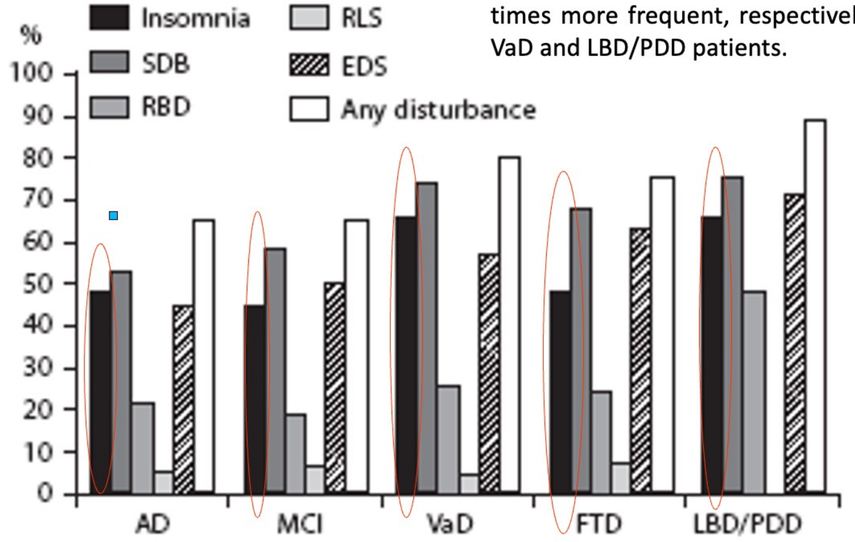
IMPLICAZIONI CLINICHE DEI NUOVI CRITERI DIAGNOSTICI

Classificazioni dell' insonnia
(DSM-5 2013,ICSD-3 2014)
Con le recenti pubblicazioni del DSM-5 e della ICSD-3, *viene superata la distinzione tra insonnie primarie e secondarie* *(dipendenti da altri disturbi medici e mentali) a favore di un 'unica categoria diagnostica*

Il Disturbo da Insonnia
***Si manifesta come condizione indipendente o in comorbidità* con altri disturbi mentali, medici e del sonno, per cui va sempre trattato.**

Per quanto riguarda l'estensione della pratica clinica anche all'insonnia in comorbidità, questo riconosce che le caratteristiche cliniche dell'insonnia possano essere il risultato di un processo patogenetico concomitante, ma le indicazioni al trattamento non devono modificarsi (Edinger et al., 2011).

Insomnia frequency was identical in AD and FTD patients but was about 2.5 and 1.5 times more frequent, respectively, in VaD and LBD/PDD patients.



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Fenotipi di Insonnia

- Difficoltà ad iniziare il sonno
- Sonno interrotto
- Risveglio precoce

- Disturbi diurni

Sindrome delle apnee ostruttive in sonno

OSAS is an independent risk factor for the development of cardiovascular disease, particularly hypertension, but also coronary artery disease, congestive cardiac failure and **stroke**

(ParatiG., Lombardi C., Hedner Jan et al " Position paper on the management of patients with obstructive sleep apnea and hypertension: joint recommendations by the European Society of Hypertension, by the European Respiratory Society and by members of the european COST ACTION B26 on obstructive sleep apnea" J Hypertens 30: 633-646, **2012**)

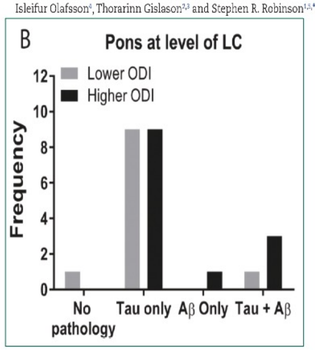
Alta prevalenza di OSA nella VaD

SLEEP, 2021, 1–12

ORIGINAL ARTICLE

Alzheimer's disease neuropathology in the hippocampus and brainstem of people with obstructive sleep apnea

Jessica E. Owen[1,*], Bryndis Benediktsdottir[2,3], Elizabeth Cook[1], Isleifur Olafsson[4], Thorarinn Gislason[2,3] and Stephen R. Robinson[1,5,*]



Age main predictor of TAU burden
OSA severity

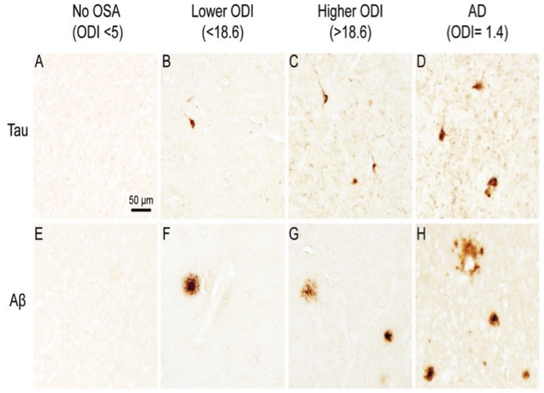
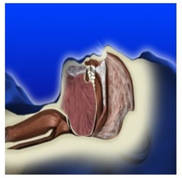


Figure 3. Micrographs of hippocampus sections from people with OSA. A person with no OSA (A, E), lower ODI (B, F), higher ODI (C, G), or AD (D, H). Tau staining indicates NFT (A–D) and Aβ staining indicates amyloid plaques (E–H).

the spatiotemporal spread of pathogenesis is identical for AD and OSA.

Effetto facilitante dell'OSA sulla neuropatologia AD, non condizione necessaria e sufficiente per causare AD



Sleep-disordered breathing advances cognitive decline in the elderly

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Tyler Gumb, BA
Elizabeth Pirraglia, MA
Andrew W. Varga, PhD, MD
Shou-en Lu, PhD
Jason Lim, BA
Margaret E. Wohlleber, BA
Emma L. Ducca, BA
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Lidia Glodzik, MD
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Indu Ayappa, PhD
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For the Alzheimer's Disease Neuroimaging Initiative

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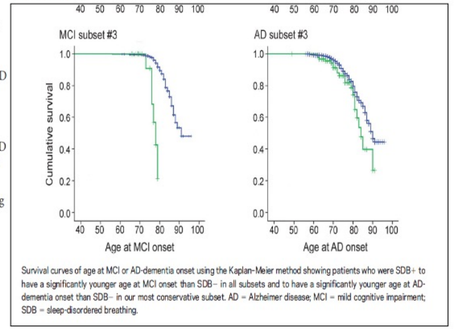
ABSTRACT

Objective: To examine whether the presence of sleep-disordered breathing (SDB) is associated with an earlier age at mild cognitive impairment (MCI) or Alzheimer disease (AD)-dementia onset in participants from the Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort. We also examined whether continuous positive airway pressure (CPAP) use is associated with delayed onset of cognitive decline.



Survival curves of age at MCI or AD-dementia onset using the Kaplan-Meier method showing patients who were SDB+ to have a significantly younger age at MCI onset than SDB− in all subsets and to have a significantly younger age at AD-dementia onset than SDB− in our most conservative subset. AD = Alzheimer disease; MCI = mild cognitive impairment; SDB = sleep-disordered breathing.

2015
AD NI database
3 subsets with progressive more stringent criteria

Age at MCI or AD-dementia onset was the main outcome variable

ADNI (Alzheimer Disease Neuroimaging Initiative)

Cognitive dysfunction in patients with obstructive sleep apnea (OSA): partial reversibility after continuous positive airway pressure (CPAP)

L. Ferini-Strambi*, C. Baietto, M.R. Di Gioia, P. Castaldi, C. Castronovo, M. Zucconi, S.F. Cappa

Brain Research Bulletin 61 (2003) 87–92

At baseline,OSA patients had a significant impairment, compared to controls, in tests of sustained attention, visuospatial learning, executive function, motor performance, and constructional abilities.

After a 15-days CPAP treatment attentive, visuospatial learning, and motor performances returned to normal levels.

A 4-months CPAP treatment did not result in any further improvement in cognitive tests.

Performance on tests evaluating executive functions and constructional abilities was not affected by short- and long-term treatment with CPAP.

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Journal of Alzheimer's Disease Reports 5 (2021) 515–533
DOI 10.3233/ADR-210304
IOS Press

Review

The Importance of Diagnosing and the Clinical Potential of Treating Obstructive Sleep Apnea to Delay Mild Cognitive Impairment and Alzheimer's Disease: A Special Focus on Cognitive Performance

Mariana Fernandes[a], Fabio Placidi[a,b], Nicola Biagio Mercuri[b,c] and Claudio Liguori[a,b,*]

Experimental Brain Research (2021) 239:3537–3552
https://doi.org/10.1007/s00221-021-06225-2

RESEARCH ARTICLE

Cognition effectiveness of continuous positive airway pressure treatment in obstructive sleep apnea syndrome patients with cognitive impairment: a meta-analysis

Xinzhao Jiang[1] · Zicong Wang[1] · Nan Hu[1,3] · Ying Yang[1] · Rui Xiong[1] · Zhengqi Fu[2]

Received: 12 July 2021 / Accepted: 14 September 2021 / Published online: 21 September 2021

Nella decisione del trattamento di una OSAS è necessario valutare non solo le complicanze mediche (cardiovascolari) dell' OSAS, ma anche le conseguenze neuropsicologiche: le alterazioini neurobiologiche alla base di queste ultime potrebbero infatti divenire irreversibili se si dilaziona il trattamento.

I medici che si occupano di medicina del sonno dovrebbero routinariamente indagare le funzioni neuropsicologiche dei pazienti con OSAS con particolare attenzione alle funzioni esecutive.

Per contro, gli individui che mostrano disfunzioni cognitive, specie esecutive, dovrebbero ricevere uno screening per la ricerca di disturbi respiratori sonno-correlati.

Una importante implicazione è la inderogabilità di una maggiore educazione sanitaria all' OSAS sia del pubblico che dei medici per evitare l' ancora frequente misconoscimento della patologia e la conseguente esposizione dei pazienti non trattati o tardivamente trattati alle complicanze della malattia.

Prevalence of sleep disturbances in mild cognitive impairment and dementing disorders. A multicenter Italian clinical cross-sectional study on 431 patients
B. Guarnieri, Dement Geriatr Cogn, 2012

	Diagnosis	
	*AD**	*LB/PD*
Insomnia	98 (48.5) **1**	14 (66.7) **[1.4; 5.2-1.1]**
High risk for SDB	110 (53.9) **1**	16 (76.2) **[1.7; 0.6-5.2]**
Clinically probable RBD	43 (21.6) **1**	10 (47.6) **[2.6; 1.0-7.1]**
Restless Leg Syndrome	13 (6.4) **1**	0 (.0) -
Excessive daytime sleepiness	89 (44.5) **1**	15 (71.4) **[2.8; 0.9-8.1]**
Any sleep disturbance	134 (65.7) 1	19 (90.0) **[2.6; 0.5-12.3]**

* reference category
Numbers in round bracketts are percentage with the disturbance within the diagnostic group. Numbers in squared bracketts are relative risks estimated as odds ratios and 95 % confidence interval. The estimates are adjusted for age, sex, MMSE and Beck Depression Inventory score.

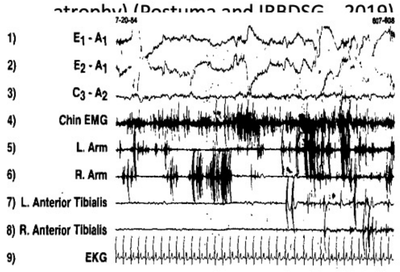
REM sleep behavior disorder (RBD)

- RBD is a **parasomnia** characterized by abnormal behaviors and **loss of the atonia during REM sleep** . RBD patients seem to **act out their dreams**, which are typically vivid and violent, through simple and/or complex motor behavior
- **Video-PSG is** required for the diagnosis .
- **Isolated** (iRBD) if not associated with other conditions such as: neurodegenerative disorders, narcolepsy type 1, autoimmune or paraneoplastic disease, brainsteam lesions or due to medications (mainly serotonin-norepinephrine reuptake inhibitor or beta-blockers)
- Polysomnography confirmed iRBD is associated with rates of phenoconv
91% over 14-year follow up l er , m
synucleinopathy (Parkinson's di dies and
atrophy) (Postuma and IRBDSG , 2019)

Chronic Behavioral Disorders of Human REM Sleep: A New Category of Parasomnia

Carlos H. Schenck, Scott R. Bundlie, Milton G. Ettinger, and Mark W. Mahowald

Sleep, Vol. 9, No. 2, 1986



RBD e demenza

In 110 pazienti con PD il sottogruppo RBD presentava alterazione delle funzioni esecutive rispetto ai pazienti senza RBD o Allucinazioni (Sinforiani et al. Mov Disorder 2006)

In PD senza demenza i 18 con RBD presentavano rispetto ai 16 non RBD peggiori prestazioni per memoria episodica verbale, funzioni escutive, visuospaziali e visuoprcettive (Vendette et al. Neurology 2007)

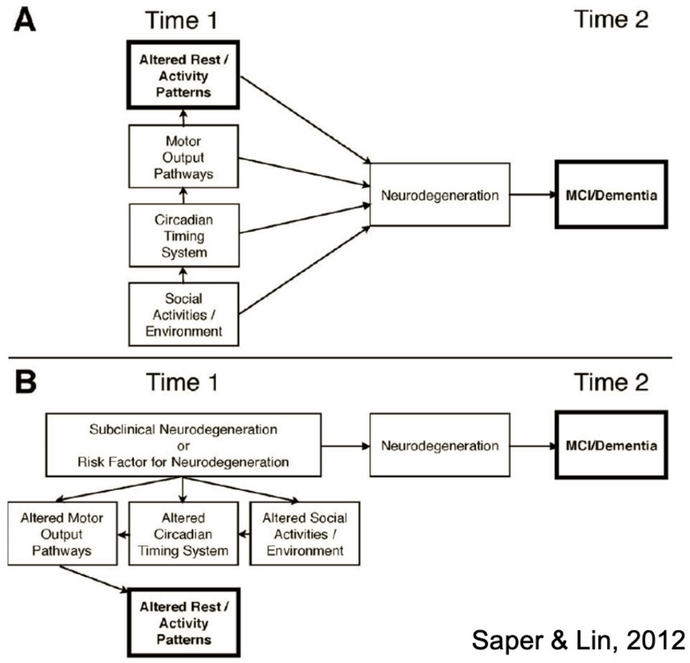
Su 65 PD con e senza RBD, il 77% aveva demenza nel gruppo con RBD e il 27% nel gruppo senza RBD e la demenza compariva più precocemente nel gruppo con RBD.

RBD predittivo per sviluppo di demenza a lungo termine

48% di pazienti MP RBD+ sviluppavano demenza a 4 anni rispetto allo 0% degli RBD- (Postuma et al., 2012)

Rischio raddoppiato di sviluppare MCI/Parkinson entro 4 anni (*Boot et al., 2012).*

ANNALS *of Neurology*



Saper & Lin, 2012

Sleep Med Rev 2018

Sleep disturbances increase the risk of dementia: A systematic review and meta-analysis

Shi LChen SJ Ma MY Bao YPHan Y Wang YM Shi J Vitiello MVLu L.

- overall sleep disturbances, their subtypes (e.g., insomnia, sleep disordered breathing [SDB]), and other sleep problems (e.g., excessive daytime sleepiness, sleep-related movement disorder, circadian rhythm sleep disorder, and nonspecific sleep problems) / incident all-cause dementia and **Alzheimer's disease (AD) and vascular dementia subtypes**.
- systematic search of the PubMed, EMBase, ISI Web of Science, and PsycINFO databases for **longitudinal studies** that were published **up to October 28, 2016.**
- **12,926 papers retrieved**.
- **Eighteen longitudinal studies** that included 246,786 subjects at baseline and 25,847 dementia cases after an average 9.49 y of follow-up were eligible for inclusion.
- **Compared with individuals without sleep disturbances, subjects who reported sleep disturbances had a higher risk of incident all-cause dementia, AD, and vascular dementia.**
- **The subgroup analysis showed that insomnia increased the risk of AD but not vascular or all-cause dementia**
- **SDB was associated with a higher incidence of all-cause dementia, AD, and vascular dementia.**
- This meta-analysis suggests that **sleep disturbances may predict the risk of incident dementia.**

SLEEP FRAGMENTATION AND RISK OF ALZHEIMER DISEASE AND COGNITIVE DECLINE

http://dx.doi.org/10.5665/sleep.2802

Sleep Fragmentation and the Risk of Incident Alzheimer's Disease and Cognitive Decline in Older Persons

Andrew S. P. Lim, MD[1]; Matthew Kowgier, PhD[2]; Lei Yu, PhD[3,4]; Aron S. Buchman, MD[3,4]; David A. Bennett, MD[3,4]

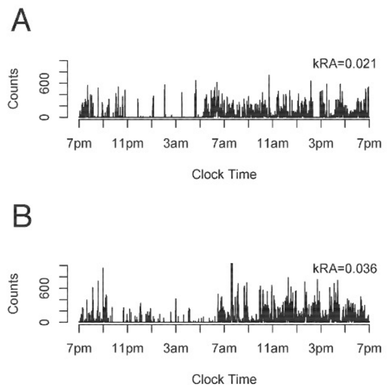


Figure 1—Illustrative actigraphic recordings. 24 h of actigraphy from two representative participants at the 10th (Panel A; k_{RA} 0.021) and 90th (Panel B; k_{RA} 0.036) percentiles of sleep fragmentation.

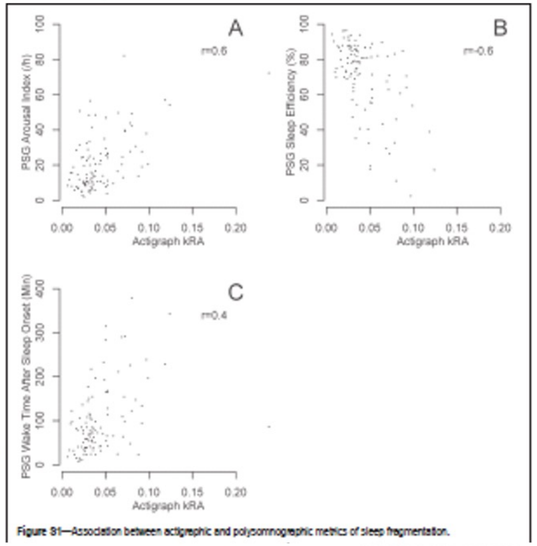


Figure 8—Association between actigraphic and polysomnographic metrics of sleep fragmentation.

SLEEP 2013;36(7):1027-1032.

SLEEP FRAGMENTATION AND RISK OF ALZHEIMER DISEASE AND COGNITIVE DECLINE

http://dx.doi.org/10.5665/sleep.2802

Sleep Fragmentation and the Risk of Incident Alzheimer's Disease and Cognitive Decline in Older Persons

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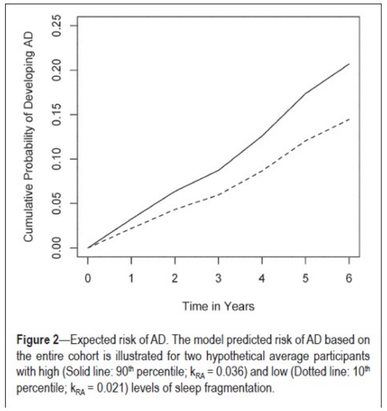


Figure 2—Expected risk of AD. The model predicted risk of AD based on the entire cohort is illustrated for two hypothetical average participants with high (Solid line: 90th percentile; k_{RA} = 0.036) and low (Dotted line: 10th percentile; k_{RA} = 0.021) levels of sleep fragmentation.

I soggetti con elevata frammentazione presentano un rischio di sviluppare demenza di 1,5 volte maggiore rispetto a chi non ha frammentazione

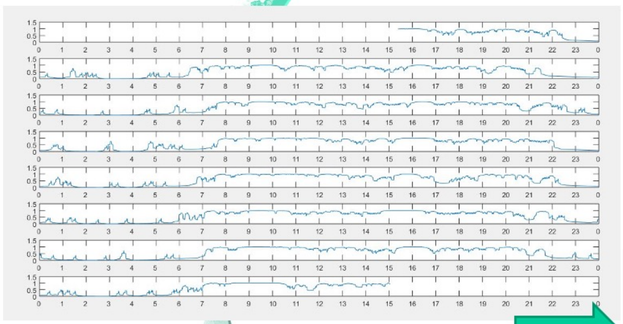
L'incremento di 0,01 unità della frammentazione del sonno era associato a un incremento annuale del 22 % del rischio di declino cognitivo

SLEEP 2013;36(7):1027-1032.

SLEEP REGULARITY INDEX (

Average activity and sleep –wake paramete

Based on " Dormi " algorhithm *by Faraguna U.*



$$-100 + \frac{200}{M(N-1)} \sum_{j=1}^{M} \sum_{i=1}^{N-1}$$

where $\delta(s_{ij}, s_{i+1,j}) = 1$ if $s_{ij} = s_{i+1,j}$ and 0 otherwise.

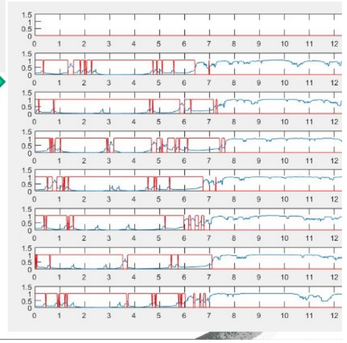
Regarding other sleep-related variables, sleep duration (tota
(24-hour) sleep time in minutes in equation (2), i.e.

$$\sum_{i,j} s_{ij} \times 0.5 \text{ minutes}/$$

Sleep midpoint, our index of sleep timing, was calculated as
of day) using the following equation (3), where t_j denotes time

$$\frac{1440}{2\pi} \arctan 2 \left(\sum_{j=1}^{M} \sum_{i=1}^{N} s_{ij} \sin \frac{2\pi t_j}{1440} +$$

Finally, average daily activity was calculated as the sum of al



Blue line : the instantaneous probability that « Dormi» algorythm extimates Wake(1) or Sleep(0) for each 1 minute epoch

SRI : intra and inter daily S-W variability

Shapiro-Wilk
ANOVA two ways

WOMEN

Group	N	Mean	SD	SEM
SRI F CTRL	35	69,781	11,396	1,926
SRI F PZ	46	69,182	11,183	1,649

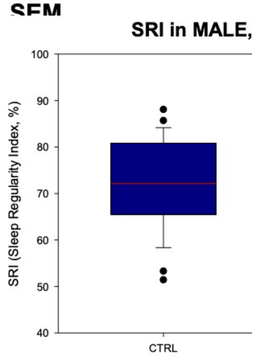
There is not a statistically significant difference (**P = 0,813**).

MEN

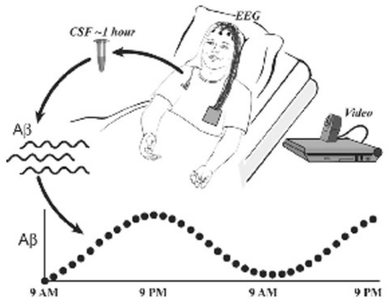
Group	N	Mean	SD	SEM
SRI M CTRL	29	72,128	9,494	
SRI M PZ	36	65,898	9,454	

There is a statistically significant difference (**P = 0,011**).

MCI -MEN more intra and inter daily S-W variability
as compared to controls



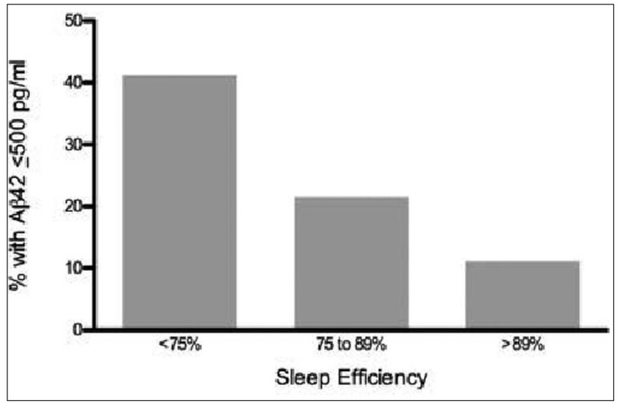
Gli studi che hanno esaminato i biomarker associati alla malattia di Alzheimer hanno mostrato che una ridotta qualità del sonno potrebbe avere un ruolo nella demenza.



ORIGINAL CONTRIBUTION

Sleep Quality and Preclinical Alzheimer Disease

Yo-El S. Ju, MD; Jennifer S. McLeland, MSW, MA; Cristina D. Toedebusch, BS; Chengjie Xiong, PhD; Anne M. Fagan, PhD; Stephen P. Duntley, MD; John C. Morris, MD; David M. Holtzman, MD



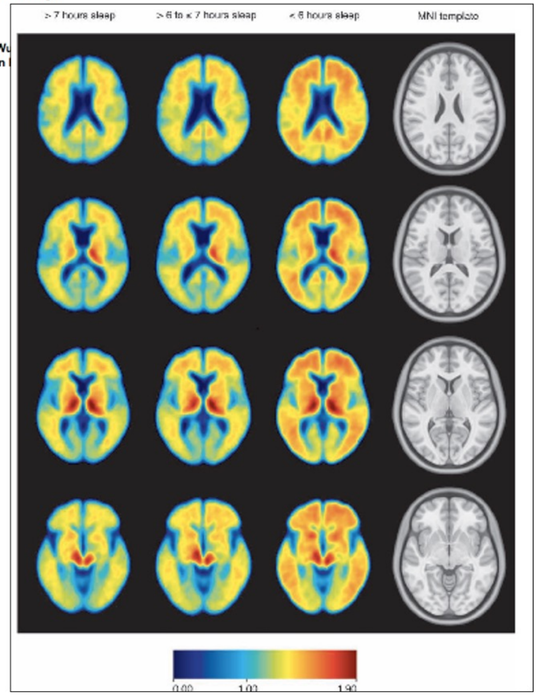
in 142 anziani cognitivamente sani, una bassa efficienza del sonno è associata con l'aumento dei depositi di amiloide cerebrale misurati con le basse concentrazioni di B amiloide liquorale

30

Self-Reported Sleep and β-Amyloid Deposition in Community-Dwelling Older Adults

Adam P. Spira, Ph.D.[1], Alyssa A. Gamaldo, Ph.D.[2], Yang An, M.S.[2], Mark N. Wu[3], Eleanor M. Simonsick, Ph.D.[2], Murat Bilgel, B.S.[2,4], Yun Zhou, Ph.D.[5], Dean F. M.D., Ph.D.[5,6], Luigi Ferrucci, M.D., Ph.D.[2], and Susan M. Resnick, Ph.D.[2]

La pet con tracciante per l'amiloide in questo caso PIB ha evidenziato una associazione tra carico di amiloide e durata soggettiva del sonno.
Chi dorme 6-7 ore ha un carico intermedio rispetto a chi ne dorme più di 7 e meno di 6



JAMA Neurol. Author manuscript; available in PMC 2014 December 01.

Published in final edited form as:
JAMA Neurol. 2013 December 1; 70(12): . doi:10.1001/jamaneurol.2013.4215.

Sleep Modifies the Relation of *APOE* to the Risk of Alzheimer Disease and Neurofibrillary Tangle Pathology

Andrew S.P. Lim, MD[1], Lei Yu, PhD[2], Matthew Kowgier, PhD[3], Julie A. Schneider, MD[2], Aron S. Buchman, MD[2], and David A. Bennett, MD[2]

Studio prospettico longitudinale, follow-up 6 anni
698 soggetti
Valutazione annuale con actigrafo
98 hanno sviluppato demenza

Una migliore consolidazione del sonno attenua l'effetto dell'allele APOE ε4 :
-sul rischio di incidenza di demenza e declino cognitivo.
-sulla densità dei grovigli neurofibrillari nei soggetti deceduti

Circadian Activity Rhithms and Risk of incident Dementia and Mild Cognitive Impairment in Older Women

(Tranah et al., Annals Neurology 2011)

1282 donne partecipanti allo Study of Osteoporotic Fractures (età media 83 anni)

Actigrafia e valutazione neuropsicologica basalmente e dopo follow up a 4,9 anni.

Follow-up: 195 demenza (15%), 302 MCI (24%).

Rischio aumentato (no fattori confondenti) per sviluppo MCI o demenza :

- Minore ampiezza dei ritmi circadiani
- Minore robustezza dei ritmi circadiani
- Acrofase ritardata

33

Sleep-Disordered Breathing, Hypoxia, and Risk of Mild Cognitive Impairment and Dementia in Older Women

Yaffe et al., JAMA, 2011

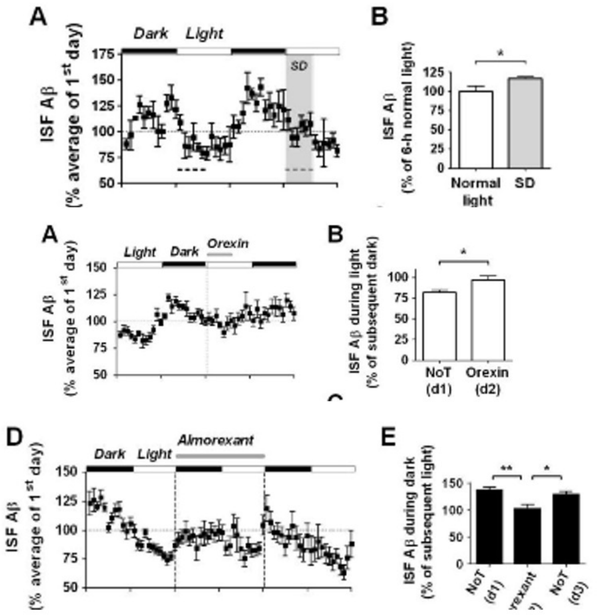
Studio prospettico su 5 anni di 298 donne senza demenza (età media 82,3 ±3,2 aa).

Un DRS;
un indice di apnea ipopnea>15;
o un tempo di sonno in apnea>7%,
correlano con il rischio di rischio di MCI o demenza al follow up.

	Mild Cognitive Impairment or Dementia, No. (%) (n = 107)	OR (95% CI)	
		Unadjusted	Adjusted[a]
Hypoxia and Disordered Breathing Measures			
Oxygen desaturation index, events/h			
<15	46 (43.0)	1 [Reference]	1 [Reference]
≥15	60 (56.1)	1.67 (1.03-2.69)	1.71 (1.04-2.83)
Oxygen saturation <90%			
<1% of sleep time	64 (59.8)	1 [Reference]	1 [Reference]
≥1% of sleep time	43 (40.2)	0.87 (0.54-1.41)	0.83 (0.51-1.38)
Sleep time in apnea or hypopnea, %			
Low (median: 0.9 [range, 0-2.2])	31 (29.0)	1 [Reference]	1 [Reference]
Mid (median: 4.4 [range, 2.3-7.0])	31 (29.0)	1.00 (0.55-1.82)	1.16 (0.61-2.20)
High (median: 16.4 [range, 7.0-66.8])	45 (42.1)	1.79 (1.01-3.20)	2.04 (1.10-3.78)
Sleep Fragmentation Measures			
Arousal index, arousals/h			
Low (median: 10.1 [range, 2.4-14.5])	44 (41.1)	1 [Reference]	1 [Reference]
Mid (median: 18.2 [range, 14.6-22.6])	30 (28.0)	0.52 (0.29-0.94)	0.54 (0.29-0.98)
High (median: 33.1 [range, 22.6-66.4])	32 (29.9)	0.59 (0.34-1.06)	0.58 (0.32-1.07)
Wake after sleep onset, min			
Low (median: 40.7 [range, 2.0-61.0])	31 (29.0)	1 [Reference]	1 [Reference]
Mid (median: 82.0 [range, 62.0-105.0])	32 (29.9)	1.06 (0.58-1.94)	1.17 (0.63-2.19)
High (median: 170.6 [range, 108.0-336.0])	44 (41.1)	1.69 (0.95-3.02)	1.79 (0.97-3.29)
Sleep Duration Measure			
Total sleep time, min			
Low (median: 269.9 [range, 128.0-330.0])	41 (38.3)	1 [Reference]	1 [Reference]
Mid (median: 358.2 [range, 331.0-385.0])	29 (27.1)	0.56 (0.31-1.01)	0.58 (0.31-1.09)
High (median: 425.5 [range, 386.0-630.0])	37 (34.6)	0.83 (0.47-1.47)	0.83 (0.46-1.51)

Abbreviations: CI, confidence interval; OR, odds ratio.
[a] Adjusted for age, race, body mass index (calculated as weight in kilograms divided by height in meters squared), education level, smoking status, presence of diabetes, presence of hypertension, antidepressant use, benzodiazepine use, and use of nonbenzodiazepine anxiolytics.

Amiloid beta dynamics are regulated by orexin and the sleep-wake cycle
Kang et al., Science, 2009



Deprivazione cronica di sonno aumenta carico di placche amiloidi

Bulbo olfattorio

Corteccia piriforme

Corteccia entorinale

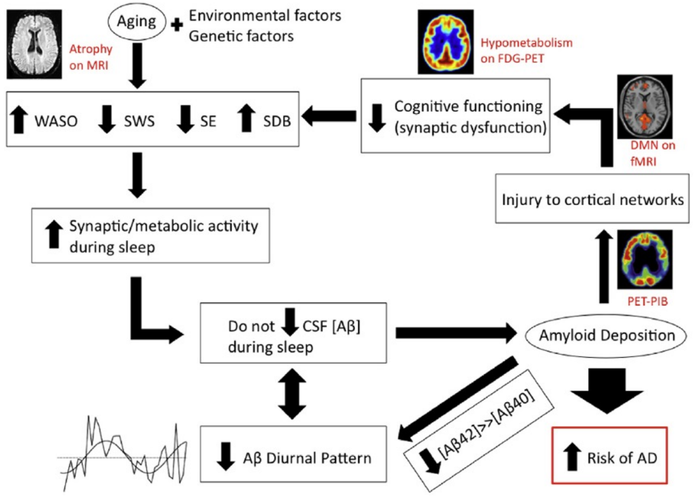
Uso di almorexant (inibitore dell'orexina) diminuisce il carico di placche amiloidi

Contents lists available at ScienceDirect
Neurobiology of Aging
journal homepage: www.elsevier.com/locate/neuaging

Review

Amyloid-β diurnal pattern: possible role of sleep in Alzheimer's disease pathogenesis

Brendan P. Lucey [a,*], Randall J. Bateman [a,b,c]

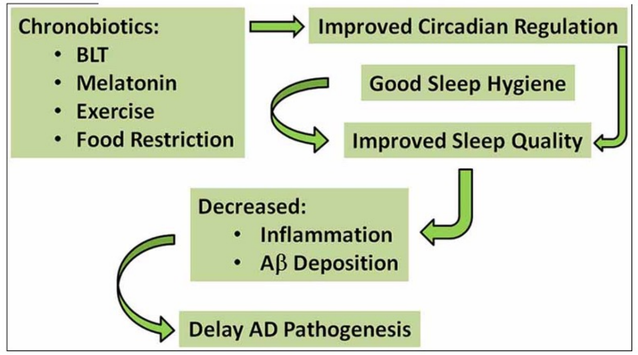


frontiers in
AGING NEUROSCIENCE
REVIEW ARTICLE
published: 08 December 2014
doi: 10.3389/fnagi.2014.00325

Buying time: a rationale for examining the use of circadian rhythm and sleep interventions to delay progression of mild cognitive impairment to Alzheimer's disease

Glenn J. Landry[1,2] *and Teresa Liu-Ambrose*[1,2,3]*

[1] Aging, Mobility, and Cognitive Neuroscience Laboratory, Department of Physical Therapy, Faculty of Medicine, University of British Columbia, Vancouver, BC, Canada
[2] Djavad Mowafaghian Centre for Brain Health, University of British Columbia, Vancouver, BC, Canada
[3] Brain Research Centre, University of British Columbia, Vancouver, BC, Canada



Un ulteriore passo avanti sarà esaminare l'effetto delle terapie per migliorare il sonno ed i ritmi circadiani nel ritardare la progressione del MCI e in generale della demenza.

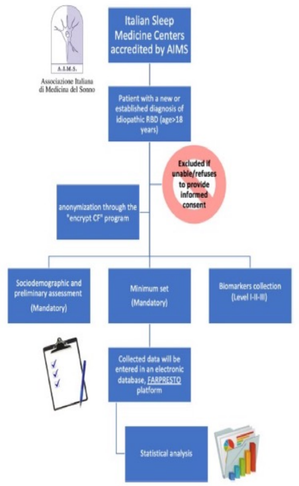
Neurological Sciences (2022) 43:6919–6928
https://doi.org/10.1007/s10072-022-06374-4

CLINICAL TRIAL ARTICLE

Predictive risk factors of phenoconversion in idiopathic REM sleep behavior disorder: the Italian study "FARPRESTO"

Monica Puligheddu[1] · Michela Figorilli[1] · Elena Antelmi[2] · Dario Arnaldi[3,4] · Elisa Casaglia[1] · Ernesto d'Aloja[5] · Luigi Ferini-Strambi[7,8] · Raffaele Ferri[9] · Gian Luigi Gigli[10] · Francesca Ingravallo[5] · Michelangelo Maestri[11] · Michele Terzaghi[12,13] · Giuseppe Plazzi[14,15] · and the FARPRESTO Consortium

Fig. 1 FARPRESTO study design. FARPRESTO study design flowchart (Source clipart: cliparts-library.com)

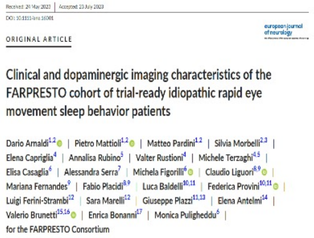


Received: 24 May 2023 | Accepted: 23 July 2023
DOI: 10.1111/ene.16001
european journal of neurology
ORIGINAL ARTICLE

Clinical and dopaminergic imaging characteristics of the FARPRESTO cohort of trial-ready idiopathic rapid eye movement sleep behavior patients

Dario Arnaldi[1,2] | Pietro Mattioli[1,2] | Matteo Pardini[1,2] | Silvia Morbelli[2,3] | Elena Capriglia[4] | Annalisa Rubino[5] | Valter Rustioni[4] | Michele Terzaghi[4,5] | Elisa Casaglia[6] | Alessandra Serra[7] | Michela Figorilli[6] | Claudio Liguori[8,9] | Mariana Fernandes[9] | Fabio Placidi[8,9] | Luca Baldelli[10,11] | Federica Provini[10,11] | Luigi Ferini-Strambi[12] | Sara Marelli[12] | Giuseppe Plazzi[11,13] | Elena Antelmi[14] | Valerio Brunetti[15,16] | Enrica Bonanni[17] | Monica Puligheddu[6] | for the FARPRESTO Consortium

- 365 patients were enrolled, and 289 patients with follow-up (age 67.7 ± 7.3 years, 237 males, mean follow-up 40 ± 37 months) were included in this study.
- At follow-up, 97 iRBD patients (33.6%) phenoconverted to an overt synucleinopathy.



Received: 29 Mar 2021 | Accepted: 23 July 2021
DOI: 10.1111/ene.15091
ORIGINAL ARTICLE
european journal of neurology

Clinical and dopaminergic imaging characteristics of the FARPRESTO cohort of trial-ready idiopathic rapid eye movement sleep behavior patients

Dario Arnaldi[1,2] | Pietro Mattioli[1,2] | Matteo Pardini[1,2] | Silvia Morbelli[2,3] | Elena Caprigila[4] | Annalisa Rubino[5] | Valter Rustioni[4] | Michele Terzaghi[5,6] | Elisa Casaglia[6] | Alessandra Serra[7] | Michela Figorilli[8] | Claudio Liguori[8,9] | Mariana Fernandes[9] | Fabio Placidi[8,9] | Luca Baldelli[10,11] | Federica Provini[10,11] | Luigi Ferini-Strambi[12] | Sara Marelli[12] | Giuseppe Plazzi[11,13] | Elena Antelmi[14] | Valerio Brunetti[15,16] | Enrica Bonanni[17] | Monica Puligheddu[5] | for the FARPRESTO Consortium

- Older age, motor and cognitive impairment, constipation, urinary and sexual dysfunction, depression, and visual semi-quantification of nigrostriatal functioning predicted phenoconversion.

- Of note, non-converted and newly diagnosed iRBD patients, who represent a trial-ready cohort for upcoming disease-modification trials, are currently being enrolled and followed in the FARPRESTO study.

Clinical issues

- Diagnosis
  - Probable RBD (scale) vs definite RBD (videoPSG)
- Symptomatic treatment
  - Behaviour, clonazepam, melatonin (DA agonist)
- Communicating the risks of phenoconversion

Città S. Angelo (PE)- Centro Medicina Sonno AIMS/*coordinatore*°°

Centri partecipanti

1.Bologna
2.Genova
3.Messina
4.Milano(Niguarda)
5.Milano (Auxologico) ***
6.Milano (Osp Sacco)
7.Monza
8.Pisa
9.Roma (Gemelli + Sapienza per PVT)
10.Roma(Tor Vergata) ***
11.Troina (EN)
12. Vicenza
13.Perugia (biomarcatori sierici)
14.Firenze (Don Gnocchi)(analisi statistica-gestione database)

Effetto del trattamento CPAP sulle funzioni cognitive in pazienti con MCI e AD affetti da OSA (DEMCPAP)

Tre anni di follow up

Stretta collaborazione tra membri SINdem e AIMS

°°Approvazione CE centro coordinatore aprile 2022

*** centri con approvazione CE

B. Guarnieri

DEMCPAP

Endpoint primario

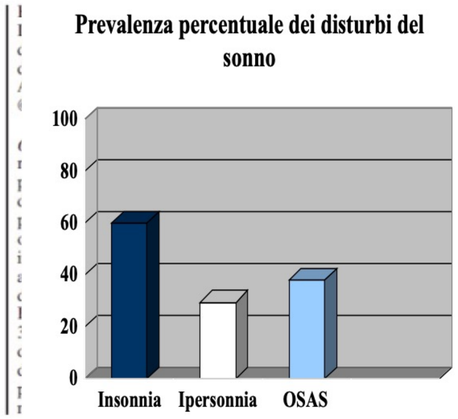
- a) Stimare **percentuale di conversione** a demenza in MCI con OSA avviati a trattamento rispetto ad MCI non avviati a trattamento e ad MCI non affetti da OSA
- b) Stimare **effetti annuali** di trattamento con CPAP sulle funzioni cognitive in pazienti MCI e AD affetti da OSA, rispetto a gruppo di controllo

- N.B. La verifica dell'**aderenza** sarà prerequisito da soddisfare per il gruppo OSA in trattamento con CPAP: la mancata/insufficiente aderenza nei primi 3 mesi di trattamento è uno dei motivi che giustifica l'assegnazione nel paziente al gruppo di controllo

Acta Neurol Scand 2010: 122: 389–397 DOI: 10.1111/j.1600-0404.2010.01324.x

ACTA NEUROLOGICA
SCANDINAVICA

Sleep disturbances in elderly subjects: an epidemiological survey in an Italian district



E. Bonanni[1], G. Tognoni[1], M. Maestri[1], N. Salvati[2], M. Fabbrini[1], D. Borghetti[1], E. Di Coscio[1], A. Choub[1], R. Sposito[1], C. Pagni[1], A. Iudice[1], L. Murri[1]

[1]Department of Neurosciences and [2]Department of Statistics and Mathematics Applied to Economy, University of Pisa, Pisa, Italy

Key words: aging; comorbidity; elderly; insomnia; OSAS; sleep, snoring

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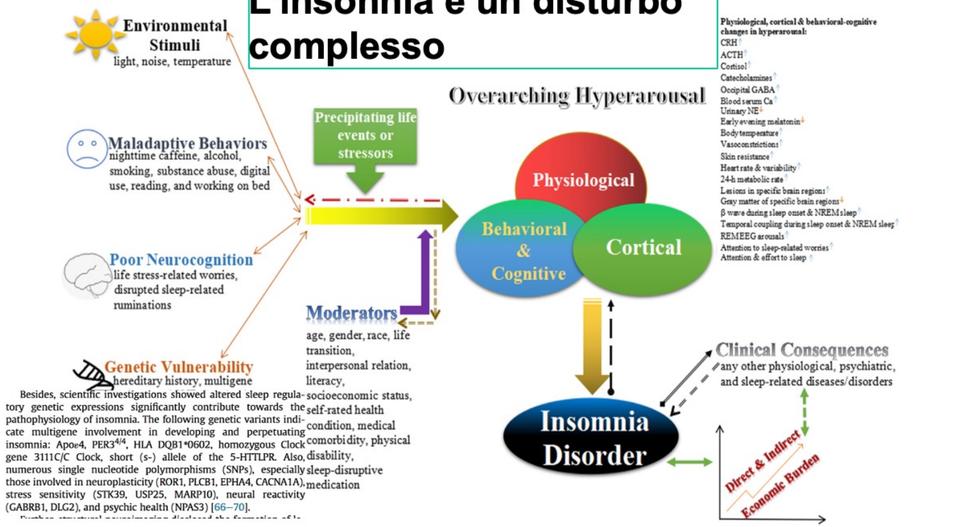
Accepted for publication December 17, 2009

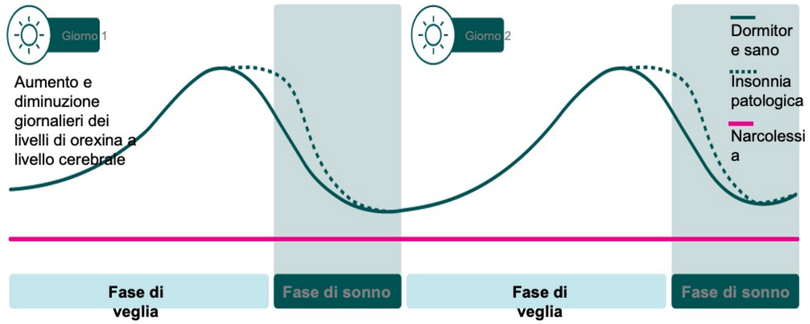
L'insonnia è un disturbo complesso



Besides, scientific investigations showed altered sleep regulatory genetic expressions significantly contribute towards the pathophysiology of insomnia. The following genetic variants indicate multigene involvement in developing and perpetuating insomnia: Apoε4, PER3$^{4/4}$, HLA DQB1*0602, homozygous Clock gene 3111C/C Clock, short (s-) allele of the 5-HTTLPR. Also, numerous single nucleotide polymorphisms (SNPs), especially those involved in neuroplasticity (ROR1, PLCB1, EPHA4, CACNA1A), stress sensitivity (STK39, USP25, MARP10), neural reactivity (GABRB1, DLG2), and psychic health (NPAS3) [66–70].

Fig. 1. A comprehensive etiopathophysiological model of insomnia disorder. SNPs = Single Nucleotide Polymorphisms; Ca= Calcium; CRH= Corticotrophin-Releasing Hormone; ACTH = Adrenocorticotropic Hormone; GABA = γ-Aminobutyric Acid; NE= Norepinephrine; NREM= Non-Rapid Eye Movement; REM = Rapid Eye Movement; EEG = Electroencephalography; ↑ = Increased compared to the control; ↓ = Decreased compared to the control.

L' iperarousal potrebbe essere sostenuto dal rilascio prolungato di orexina, che prolunga la veglia notturna[1]



- L'**iperarousal** notturno può portare a disturbi del sonno e a compromissione del funzionamento diurno[2]

1. Sun Y, *et al. Front Neurol Neurosci* 2021;45:22-37; 2. Levenson JC, *et al. Chest* 2015;147:1179-92.

Effect of a dual orexin receptor antagonist on Alzheimer's disease: Sleep disorders and cognition

Mengzhen Zhou[1] and Shi Tang[2]*

[1]Department of Neurology, The First Affiliated Hospital of Shandong First Medical University & Shandong Provincial Qianfoshan Hospital, Jinan, Shandong, China, [2]Department of Neurology, Shandong Provincial Hospital Affiliated to Shandong First Medical University, Jinan, Shandong, China

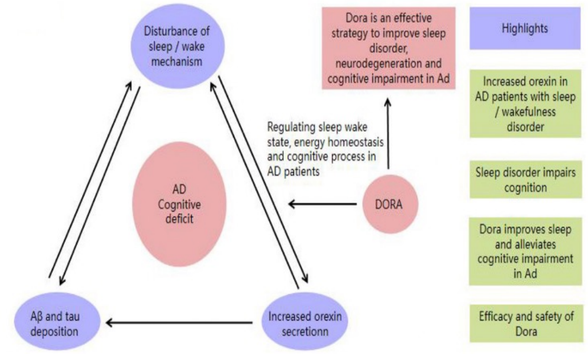


FIGURE 1
The schematic diagram of DORA intervention in AD.

Drugs & Aging
https://doi.org/10.1007/s40266-022-00977-4

ORIGINAL RESEARCH ARTICLE

Efficacy and Safety of Daridorexant in Older and Younger Adults with Insomnia Disorder: A Secondary Analysis of a Randomised Placebo-Controlled Trial

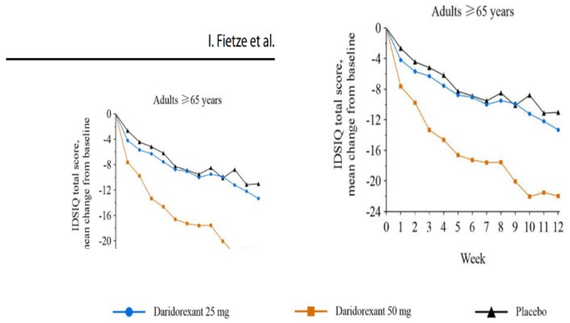
Ingo Fietze[1,2] · Claudio L. A. Bassetti[3] · David W. Mayleben[4] · Scott Pain[5] · Dalma Seboek Kinter[5] · William V. McCall[6]

Accepted: 6 September 2022

Fietze I, Bassetti CLA, Mayleben DW, Pain S, Seboek Kinter D, McCall WV. Efficacy and Safety of Daridorexant in Older and Younger Adults with Insomnia Disorder: A Secondary Analysis of a Randomised Placebo-Controlled Trial. Drugs Aging. 2022

Efficacia e sicurezza di daridorexant negli anziani-parametri soggettivi

sTST **IDSIQ-total score**



- **Miglioramento significativo di tempo di sonno soggettivo** (sTST) e **della funzionalità diurna** (IDSIQ) anche nei pazienti anziani.

La risposta al placebo è inferiore negli anziani mentre si conferma **maggiore efficacia del 50 mg** vs 25 mg.

Fietze I, Bassetti CLA, Mayleben DW, Pain S, Seboek Kinter D, McCall WV. Efficacy and Safety of Daridorexant in Older and Younger Adults with Insomnia Disorder: A Secondary Analysis of a Randomised Placebo-Controlled Trial. Drugs Aging. 2022

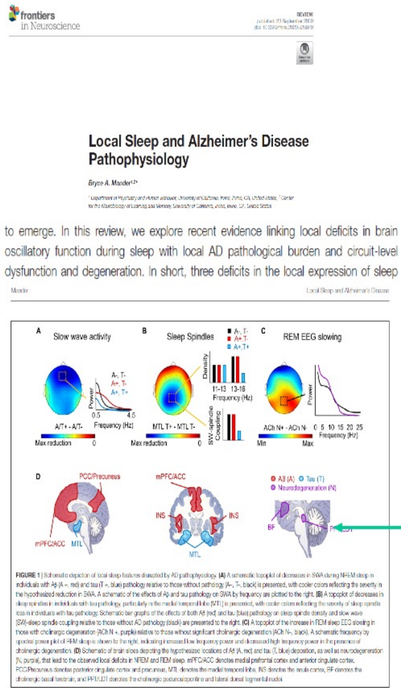
Sicurezza e tollerabilità

	<65 anni			≥65 anni		
	Daridorexant		Placebo	Daridorexant		Placebo
Caratteristiche, n (%)	**50 mg (n=189)**	**25 mg (n=189)**	**(n=187)**	**50 mg (n=119)**	**25 mg (n=121)**	**(n=122)**
Pazienti con ≥1 TEAE	74 (39)	78 (41)	67 (36)	42 (35)	39 (32)	38 (31)
Pazienti con ≥1 TEAE serio	3 (2)	1 (<1)	4 (2)	0	1 (1)	3 (3)
TEAE che hanno portato all'interruzione del trattamento	2 (1)	6 (3)	4 (2)	1 (1)	1 (1)	6 (5)
Decessi	0	0	0	0	1[a]	0
Pazienti con TEAE[b] (≥2% in qualsiasi gruppo)						
Nasofaringite						
Cefalea						
Nausea						
Affaticamento						
Overdose accidentale						
Vertigini						
Mal di schiena						
Sonnolenza						
Diarrea						
Cadute						
Influenza						
Dolore addominale superiore	0	0	0	0	3 (2,5)	1 (0,8)

Il **profilo di sicurezza** complessivo di daridorexant è risultato **simile tra gli anziani e i pazienti più giovani**, senza differenze significative nella frequenza dei singoli EA comunque bassa (<2%).

Non sono state osservate con maggiore frequenza negli anziani vertigini, sonnolenza o cadute.

Fietze I, Bassetti CLA, Mayleben DW, Pain S, Seboek Kinter D, McCall WV. Efficacy and Safety of Daridorexant in Older and Younger Adults with Insomnia Disorder: A Secondary Analysis of a Randomised Placebo-Controlled Trial. Drugs Aging. 2022



frontiers in Neuroscience

REVIEW

Local Sleep and Alzheimer's Disease Pathophysiology

Bryce A. Mander*†

to emerge. In this review, we explore recent evidence linking local deficits in brain oscillatory function during sleep with local AD pathological burden and circuit-level dysfunction and degeneration. In short, three deficits in the local expression of sleep

Mander Local Sleep and Alzheimer's Disease

FIGURE 1 | Schematic depiction of local sleep features disrupted by AD pathophysiology. (A) A schematic topoplot of decreases in SWA during NHLM sleep in individuals with Aβ (A −, red) and tau (T +, blue) pathology relative to those without pathology (A−, T−, black) is presented, with cooler colors reflecting the severity in the hypothesized reduction in SWA. A schematic of the effects of Aβ and tau pathology on SWA by frequency are plotted to the right. (B) A topoplot of decreases in sleep spindle in individuals with tau pathology, particularly in the medial temporal lobe (MTL) is presented, with cooler colors reflecting the severity of sleep spindle loss in individuals with tau pathology. Schematic bar graphs of the effects of both Aβ (red) and tau (blue) pathology on sleep spindle density and slow wave (SW)-sleep spindle coupling relative to those without AD pathology (black) are presented to the right. (C) A topoplot of the increase in REM sleep EEG slowing in those with cholinergic degeneration (ACh N +, purple) relative to those without significant cholinergic degeneration (ACh N−, black). A schematic frequency by spectral power plot of nREM sleep is shown to the right, indicating increased low frequency power and decreased high frequency power in the presence of cholinergic degeneration. (D) Schematic of brain slices depicting the hypothesized locations of Aβ (A, red) and tau (T, blue) deposition, as well as neurodegeneration (N, purple), that lead to the observed local deficits in NREM and REM sleep. mPFC/ACC denotes medial prefrontal cortex and anterior cingulate cortex, PCC/Precuneus denotes posterior cingulate cortex and precuneus, MTL denotes the medial temporal lobe, INS denotes the insula cortex, RF denotes the cholinergic basal forebrain, and PPN/LDT denotes the cholinergic pontomesencephalic and lateral dorsal tegmental nuclei.

Mander Local Sleep and Alzheimer's Disease

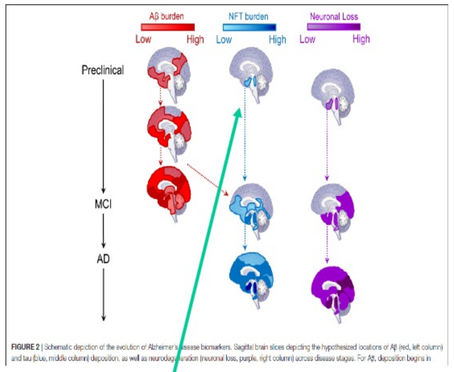


FIGURE 2 | Schematic depiction of the evolution of Alzheimer's disease biomarkers. Sagittal brain slices depicting the hypothesized locations of Aβ (red, left column) and tau (blue, middle column) deposition, as well as neurodegeneration (neuronal loss, purple, right column) across disease stages. For Aβ, deposition begins in

Wake promotion

REVIEW

Glymphatic failure as a final common pathway to dementia

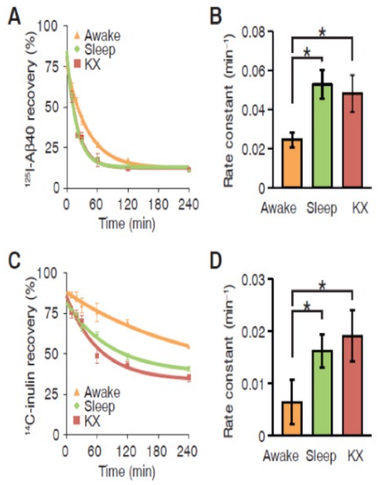
Maiken Nedergaard[1,2]* and Steven A. Goldman[1,2]*

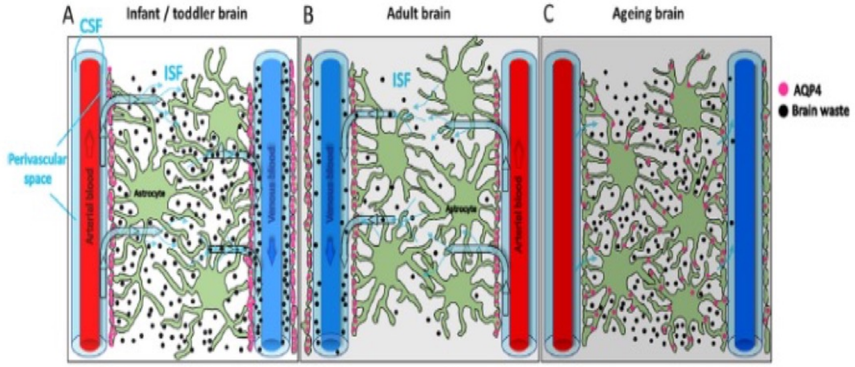
Sleep is evolutionarily conserved across all species, and impaired sleep is a common trait of the diseased brain. Sleep quality decreases as we age, and disruption of the regular sleep architecture is a frequent antecedent to the onset of dementia in neurodegenerative diseases. The glymphatic system, which clears the brain of protein waste products, is mostly active during sleep. Yet the glymphatic system degrades with age, suggesting a causal relationship between sleep disturbance and symptomatic progression in the neurodegenerative dementias. The ties that bind sleep, aging, glymphatic clearance, and protein aggregation have shed new light on the pathogenesis of a broad range of neurodegenerative diseases, for which glymphatic failure may constitute a therapeutically targetable final common pathway.

Sleep Drives Metabolite Clearance from the Adult Brain

Lulu Xie,[1]* Hongyi Kang,[1]* Qiwu Xu,[1] Michael J. Chen,[1] Yonghong Liao,[1] Meenakshisundaram Thiyagarajan,[1] John O'Donnell,[1] Daniel J. Christensen,[1] Charles Nicholson,[2] Jeffrey J. Iliff,[1] Takahiro Takano,[1] Rashid Deane,[1] Maiken Nedergaard[1]†

The conservation of sleep across all animal species suggests that sleep serves a vital function. We here report that sleep has a critical function in ensuring metabolic homeostasis. Using real-time assessments of tetramethylammonium diffusion and two-photon imaging in live mice, we show that natural sleep or anesthesia are associated with a 60% increase in the interstitial space, resulting in a striking increase in convective exchange of cerebrospinal fluid with interstitial fluid. In turn, convective fluxes of interstitial fluid increased the rate of β-amyloid clearance during sleep. Thus, the restorative function of sleep may be a consequence of the enhanced removal of potentially neurotoxic waste products that accumulate in the awake central nervous system.





- # of astrocytes in brain: low
- # of AQP4 in astrocytes: high
- AQP4 located in endfeet: Yes
- Metabolism: high
- Levels of waste production: high
- Time in sleep to clear waste products: high (10-12h)
- Overall ratio of waste production vs. clearance: good

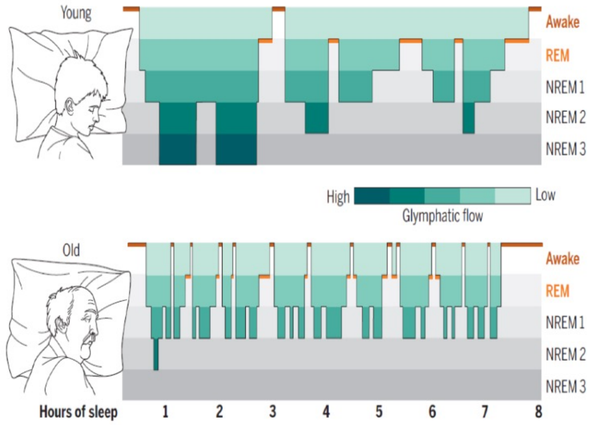
- # of astrocytes in brain: high
- # of AQP4 in astrocytes: medium
- AQP4 located in endfeet: Yes
- Metabolism: medium
- Levels of waste production: medium
- Time in sleep to clear waste products: medium (7-9h)
- Overall ratio of waste production vs. clearance: good

- # of astrocytes in brain: high
- # of AQP4 in astrocytes: medium
- AQP4 located in endfeet: No
- Metabolism: medium
- Levels of waste production: medium
- Time in sleep to clear waste products: low (4-7h)
- Overall ratio of waste production vs. clearance: bad

REVIEW

Glymphatic failure as a final common pathway to dementia

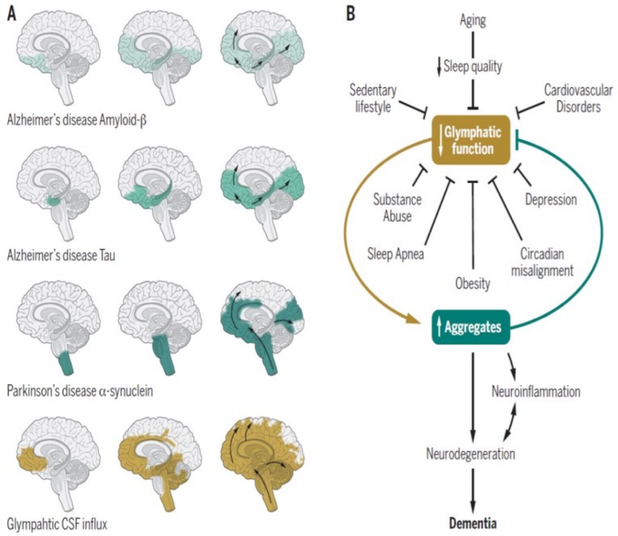
Maiken Nedergaard[1,2,*] and Steven A. Goldman[1,2,*]



REVIEW

Glymphatic failure as a final common pathway to dementia

Maiken Nedergaard[1,2,*] and Steven A. Goldman[1,2,*]



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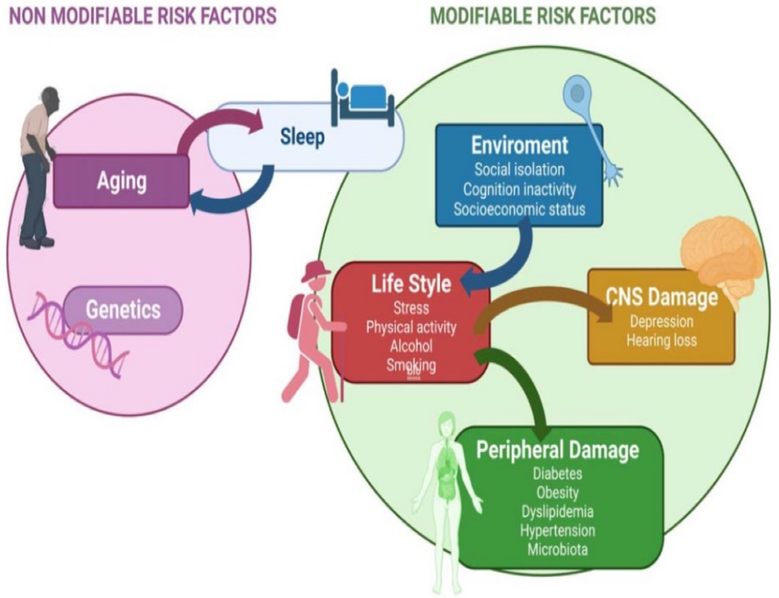

healthcare
MDPI

Review

Chronic Insomnia Disorder across Europe: Expert Opinion on Challenges and Opportunities to Improve Care

Jason Ellis [1], Luigi Ferini-Strambi [2], Diego García-Borreguero [3], Anna Heidbreder [4], David O'Regan [5,6], Liborio Parrino [7], Hugh Selsick [8] and Thomas Penzel [9,*]

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Fattori legati al medico

Sovraffollamento nelle sale d'attesa dei medici e il tempo limitato per le consultazioni medico-paziente ha impedito un esame approfondito delle singole esigenze del paziente, ostacolando il processo decisionale del trattamento.

È stato inoltre riferito ch el medici spesso mancavano di risorse e conoscenze sul trattamento dell'insonnia, in particolare nei pazienti non-responder
Gli operatori sanitari ricevono una formazione insufficiente sulla medicina del sonno sia presso gli studenti universitari che nei percorsi post-laurea

- mancanza di **linee guida nazionali**;
- assenza di un **percorso diagnostico terapeutico assistenziale (PDTA**) codificato;
- mancanza di un esplicito riferimento all'interno **dell'elenco delle malattie e condizioni croniche invalidanti** ai sensi del DPCM 12 gennaio 2017 "Definizione e aggiornamento dei livelli essenziali di assistenza, di cui all'articolo 1, comma 7, del decreto legislativo 30 dicembre 1992, n. 502";
- assenza di un esplicito riferimento all'interno della tabella di cui al decreto del Ministero della Sanità 5 febbraio 1992 "*Approvazione della nuova **tabella indicativa delle percentuali d'invalidità** per le minorazioni e malattie invalidanti**";***
- scarsa **attività di comunicazione e sensibilizzazione** rivolta a cittadini e professionisti.

-

Delitti in materia di violazione del diritto d'autore (Art. 25-novies, D.Lgs. n. 231/2001) [articolo aggiunto dalla L. n. 99/2009]

- Messa a disposizione del pubblico, in un sistema di reti telematiche, mediante connessioni di qualsiasi genere, di un'opera dell'ingegno protetta, o di parte di essa (art. 171, legge n.633/1941 comma 1 lett. a) bis)
- Reati di cui al punto precedente commessi su opere altrui non destinate alla pubblicazione qualora ne risulti offeso l'onore o la reputazione (art. 171, legge n.633/1941 comma 3)
- Abusiva duplicazione, per trarne profitto, di programmi per elaboratore; importazione, distribuzione, vendita o detenzione a scopo commerciale o imprenditoriale o concessione in locazione di programmi contenuti in supporti non contrassegnati dalla SIAE; predisposizione di mezzi per rimuovere o eludere i dispositivi di protezione di programmi per elaboratori (art. 171-bis legge n.633/1941 comma 1)
- Riproduzione, trasferimento su altro supporto, distribuzione, comunicazione, presentazione o dimostrazione in pubblico, del contenuto di una banca dati; estrazione o reimpiego della banca dati; distribuzione, vendita o concessione in locazione di banche di dati (art. 171-bis legge n.633/1941 comma 2)
- Abusiva duplicazione, riproduzione, trasmissione o diffusione in pubblico con qualsiasi procedimento, in tutto o in parte, di opere dell'ingegno destinate al circuito televisivo, cinematografico, della vendita o del noleggio di dischi, nastri o supporti analoghi o ogni altro supporto contenente fonogrammi o videogrammi di opere musicali, cinematografiche o audiovisive assimilate o sequenze di immagini in movimento; opere letterarie, drammatiche, scientifiche o didattiche, musicali o drammatico musicali, multimediali, anche se inserite in opere collettive o composite o banche dati; riproduzione, duplicazione, trasmissione o diffusione abusiva, vendita o commercio, cessione a qualsiasi titolo o importazione abusiva di oltre cinquanta copie o esemplari di opere tutelate dal diritto d'autore e da diritti connessi; immissione in un sistema di reti telematiche, mediante connessioni di qualsiasi genere, di un'opera dell'ingegno protetta dal diritto d'autore, o parte di essa (art. 171-ter legge n.633/1941)
- Mancata comunicazione alla SIAE dei dati di identificazione dei supporti non soggetti al contrassegno o falsa dichiarazione (art. 171-septies legge n.633/1941)
- Fraudolenta produzione, vendita, importazione, promozione, installazione, modifica, utilizzo per uso pubblico e privato di apparati o parti di apparati atti alla decodificazione di trasmissioni audiovisive ad accesso condizionato effettuate via etere, via satellite, via cavo, in forma sia analogica sia digitale (art. 171-octies legge n.633/1941).

Torna all'inizio