FACOLTÀ DI MEDICINA
E PSICOLOGIA

SAPIENZA
UNIVERSITÀ DI ROMA

5 GIUGNO 2019

GIORNATA SCIENTIFICA DELLA FACOLTÀ DI MEDICINA E PSICOLOGIA

Aula Capozzi
Dip.to Scienze Odontostomatologiche,
Via Caserta, 6
Roma

Quali speranze per la malattia di Alzheimer dalla ricerca del sonno?

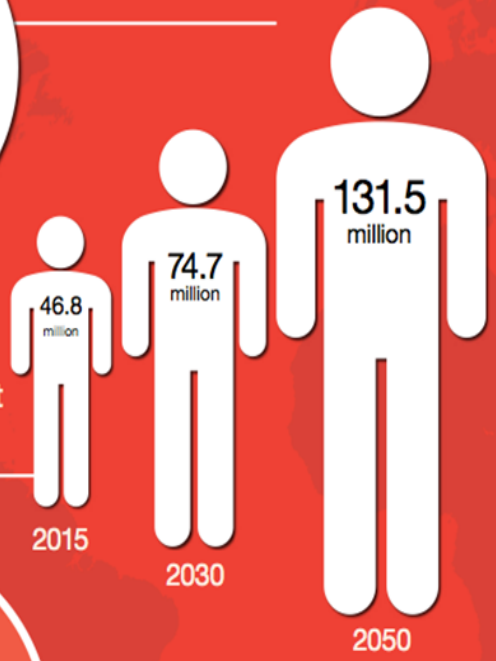
Luigi De Gennaro

INFOGRAPHIC

The global impact of dementia

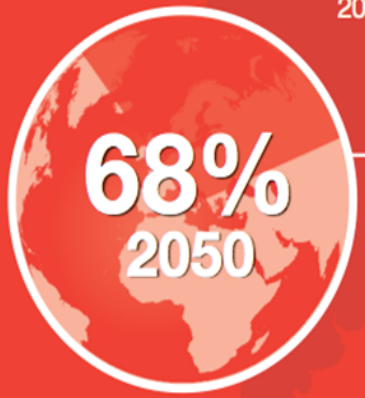
Around the world, there will be 9.9 million new cases of dementia in 2015,

one every 3 seconds

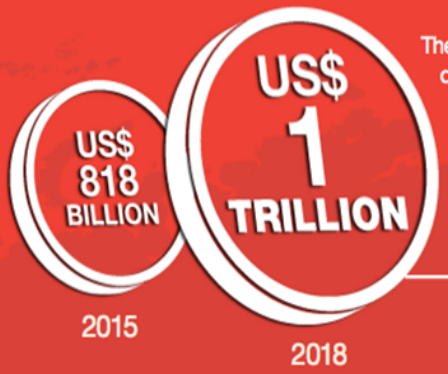


46.8 million people worldwide are living with dementia in 2015.

This number will almost double every 20 years.



Much of the increase will take place in low and middle income countries (LMICs): in 2015, 58% of all people with dementia live in LMICs, rising to 63% in 2030 and 68% in 2050.



The total estimated worldwide cost of dementia in 2015 is US$ 818 billion. By 2018, dementia will become a trillion dollar disease, rising to

US$ 2 trillion by 2030

If global dementia care were a country, it would be the

18th largest economy

in the world exceeding the market values of companies such as Apple and Google

(source: Forbes 2015 ranking).

This map shows the estimated number of people living with dementia in each world region in 2015.

We must now involve more countries and regions in the global action on dementia.

SONNO E MALATTIA DI ALZHEIMER

1. Disturbi del sonno nei pazienti Alzheimer
2. Ruolo del sonno nell'eliminazione della proteina amiloide
3. Conseguenze della deprivazione di sonno sui livelli di amiloide
4. Il rapporto tra SWA, accumuli di amiloide, decadimento mnestico, variazioni metaboliche cerebrali

Front. Pharmacol. | doi: 10.3389/fphar.2019.00695

Sleep and β-amyloid Deposition in Alzheimer's Disease: Insights on Mechanisms and Possible Innovative Treatments

Susanna Cordone[1], Ludovica Annarumma[1], Paolo M. Rossini[2] and Luigi De Gennaro[1*]

[1]Department of Psychology, Faculty of Medicine and Psychology, Sapienza University of Rome, Italy
[2]Institute of Neurology, Catholic University of the Sacred Heart, Rome, Italy

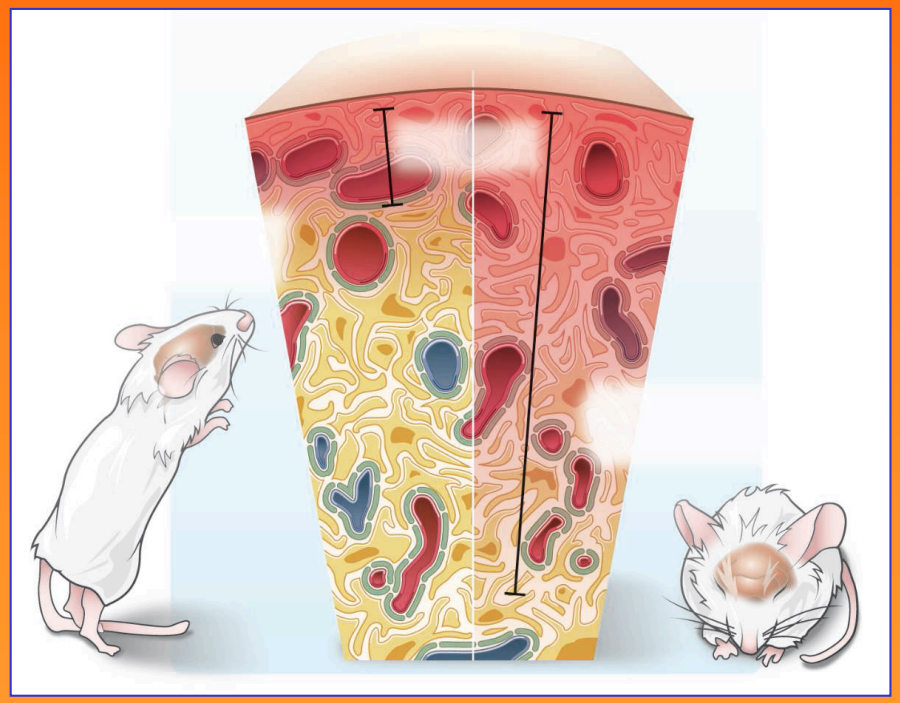
2. Ruolo del sonno nell'eliminazione della proteina amiloide

Sleep: The Brain's Housekeeper?

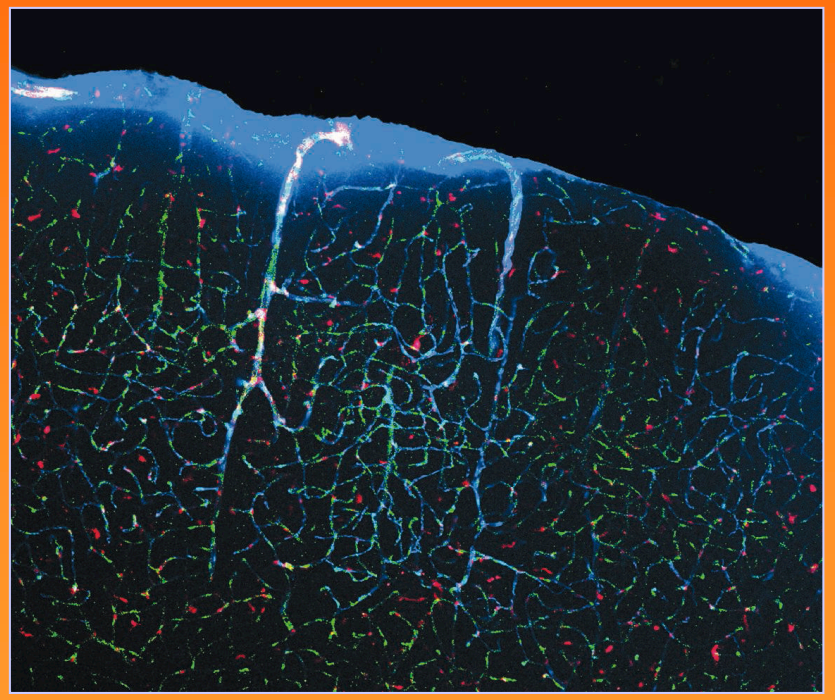
Sleep Drives Metabolite Clearance from the Adult Brain

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.



The "first direct experimental evidence at the molecular level" for what could be sleep's basic purpose: It clears the brain of toxic metabolic byproducts



Brainwashing
When mice sleep, fluid-filled channels (pale blue) between neurons expand and flush out waste

3. Conseguenze della deprivazione di sonno sui livelli di amiloide

doi:10.1093/brain/awx148 BRAIN 2017: 140; 2104–2111 | 2104

BRAIN
A JOURNAL OF NEUROLOGY

REPORT

Slow wave sleep disruption increases cerebrospinal fluid amyloid-β levels

Yo-El S. Ju,[1,2,*] Sharon J. Ooms,[3,4,5,*] Courtney Sutphen,[1,2] Shannon L. Macauley,[1,2] Margaret A. Zangrilli,[1] Gina Jerome,[1,2] Anne M. Fagan,[1,2,6] Emmanuel Mignot,[7] John M. Zempel,[1] Jurgen A.H.R. Claassen[3,4,5] and David M. Holtzman[1,2,6]

BRAIN 2017: 140; 2066–2078 | 2066

BRAIN
A JOURNAL OF NEUROLOGY

SCIENTIFIC COMMENTARIES

A restless night makes for a rising tide of amyloid

3. Conseguenze della deprivazione di sonno sui livelli di amiloide

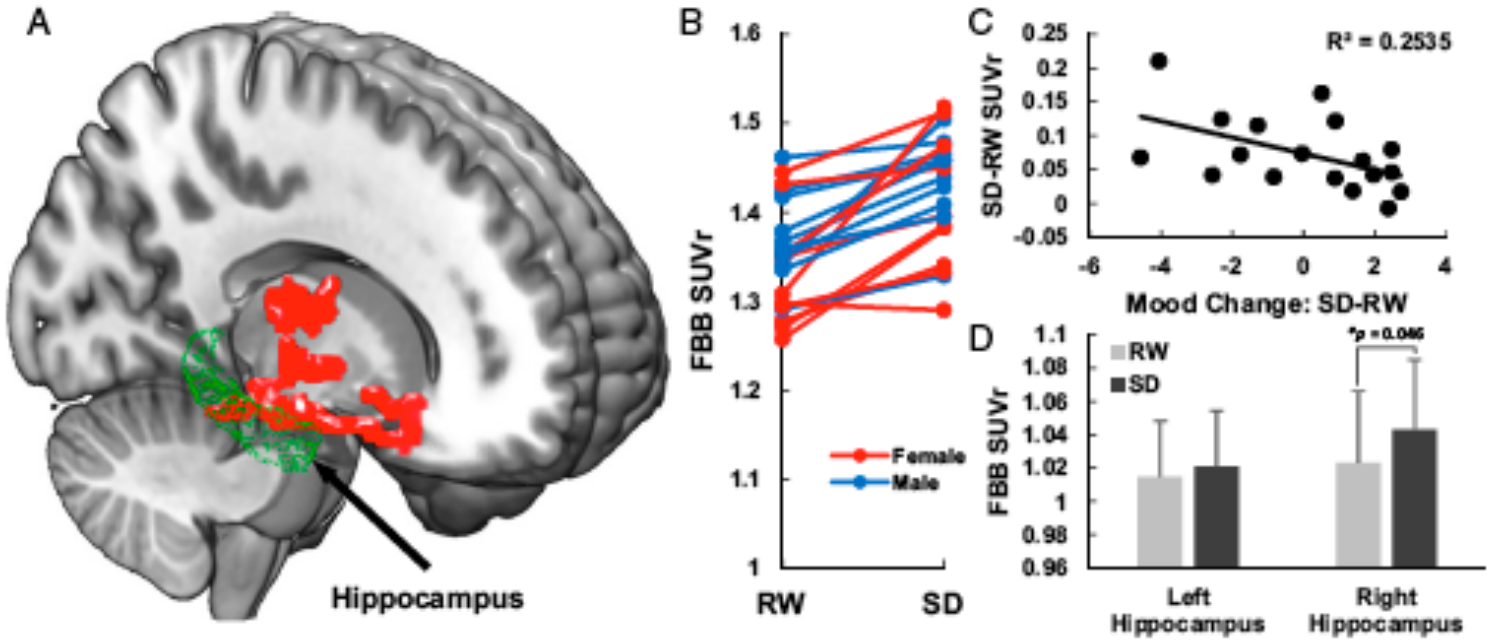


Fig. 1. Effects of one-night SD on ABB. (*A*) Voxelwise paired *t* test between RW and SD conditions highlighting the hippocampus as well as other subcortical structures ($P_{FWE} < 0.05$, cluster-size corrected) (Table S1). (*B*) Subject-level changes in FBB SUVr (in the red cluster identified in *A*) from RW to SD. There was no significant effect of gender, or gender × sleep interaction ($P > 0.15$). (*C*) Association between changes in mood from RW to SD and changes in the FBB SUVr for the cluster identified in *A*. Mood change was quantified using the principal component of the changes in self-report measures from RW to SD, which accounted for 35.5% of the variance. Self-report measures of alert, friendly, happy, social, and energetic significantly decreased, and measures of tired and difficulty staying awake significantly increased from RW to SD ($P < 0.001$, two-tailed) (see also Fig. S1). (*D*) Average FBB SUVr in a priori hippocampus ROIs across subjects. Error bars show standard deviation (*Methods*).

PNAS

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

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

[a]Laboratory of Neuroimaging, National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health, Bethesda, MD 20892; [b]Piramal Pharma Inc., Boston, MA 02108; and [c]Department of Anesthesiology, Yale School of Medicine, New Haven, CT 06510

Edited by Michael E. Phelps, University of California, Los Angeles, CA, and approved March 13, 2018 (received for review December 14, 2017)

La deprivazione di sonno si associa si associa a un incremento di amiloide, principalmente a livello ippocampale e talamico

4. SWA, accumulo di amiloide, decadimento mnestico, variazioni metaboliche cerebrali

ARTICLES

nature neuroscience

β-amyloid disrupts human NREM slow waves and related hippocampus-dependent memory consolidation

Bryce A Mander[1], Shawn M Marks[2], Jacob W Vogel[2], Vikram Rao[1], Brandon Lu[3], Jared M Saletin[1], Sonia Ancoli-Israel[4], William J Jagust[2,5] & Matthew P Walker[1,2]

ARTICLES

nature neuroscience

Prefrontal atrophy, disrupted NREM slow waves and impaired hippocampal-dependent memory in aging

Bryce A Mander[1], Vikram Rao[1], Brandon Lu[2], Jared M Saletin[1], John R Lindquist[1], Sonia Ancoli-Israel[3], William Jagust[4,5] & Matthew P Walker[1,4]

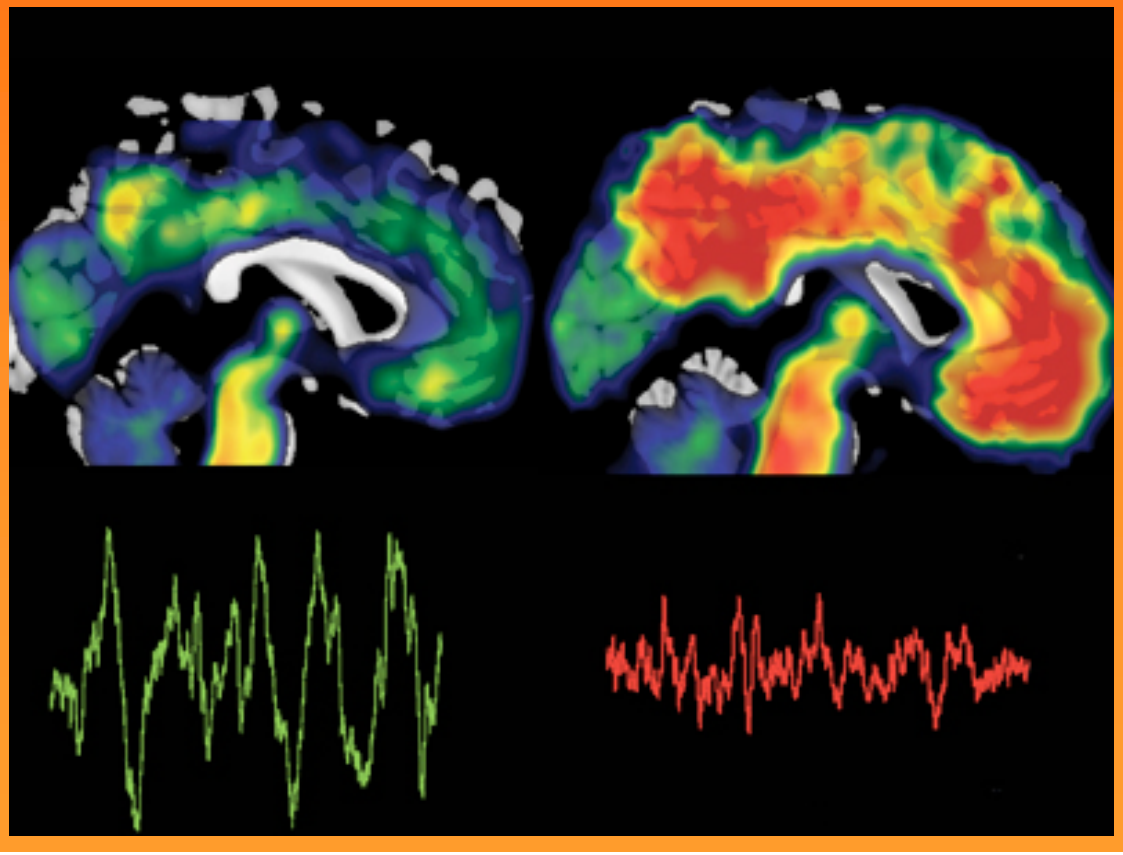
Una diretta relazione causale tra attività ad onde lente, accumulo di amiloide e decremento performance mnestiche

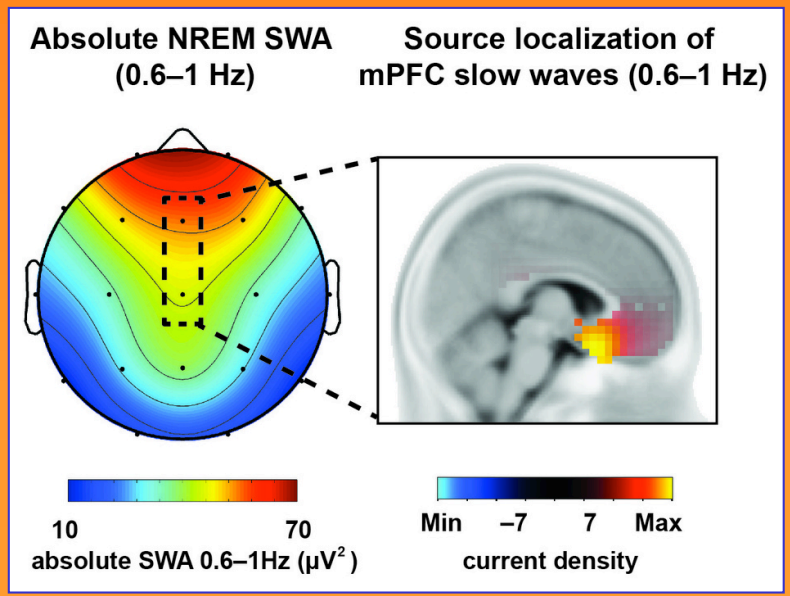
Trends in Neurosciences CellPress

Review

Sleep: A Novel Mechanistic Pathway, Biomarker, and Treatment Target in the Pathology of Alzheimer's Disease?

Bryce A. Mander,[1,*] Joe Winer,[1] William J. Jagust,[2,3] and Matthew P. Walker[1,2,*]





Ma, è lecito chiedersi, tutto ciò si estende anche alla patologia?

www.nature.com/scientificreports

SCIENTIFIC REPORTS

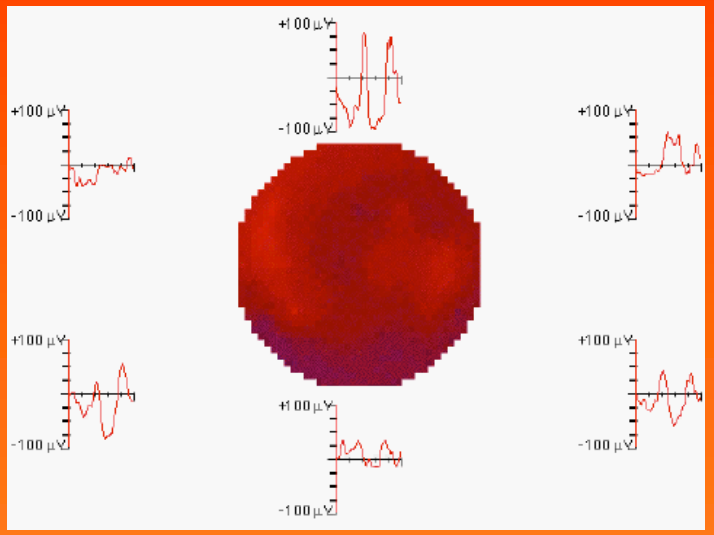
OPEN

The Fall of Sleep K-Complex in Alzheimer Disease

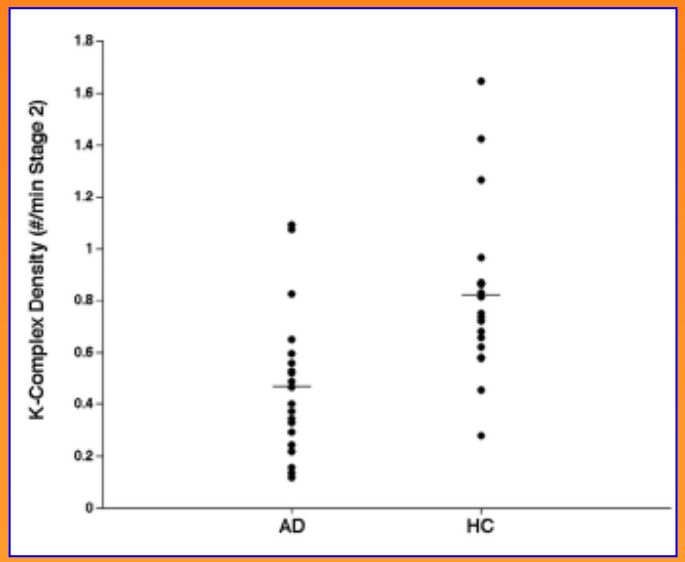
Luigi De Gennaro[1], Maurizio Gorgoni[1], Flaminia Reda[1], Giulia Lauri[1], Ilaria Truglia[1], Susanna Cordone[1], Serena Scarpelli[1], Anastasia Mangiaruga[1], Aurora D'atri[1], Giordano Lacidogna[2], Michele Ferrara[3], Camillo Marra[2] & Paolo Maria Rossini[2,4]

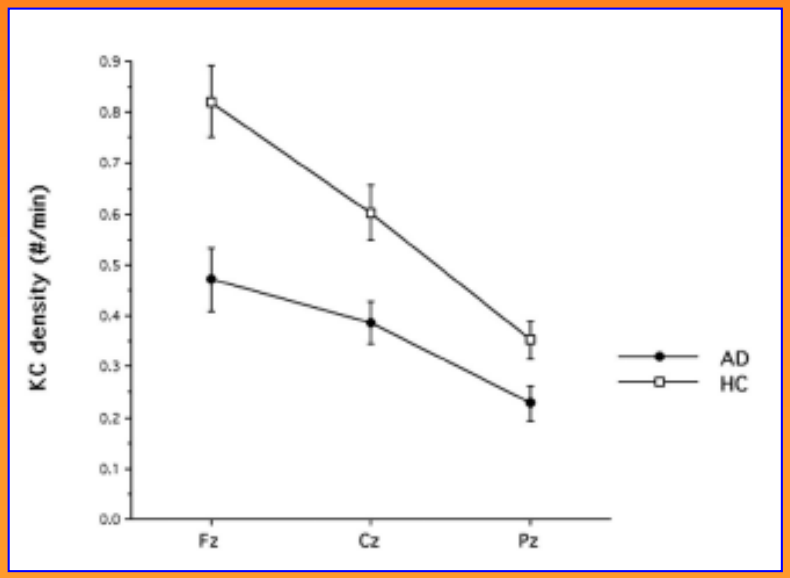
Received: 23 June 2016

Variables	AD	HC	$t_{1,38}$	p
	Mean (SE)	Mean (SE)		
Stage 1 latency (min)	51.02 (13.43)	21.45 (4.96)	**2.07**	**0.05**
Stage 2 latency (min)	42.88 (13.21)	14.15 (3.79)	**2.09**	**0.04**
Stage 1 (%)	11.59 (2.39)	6.71 (1.04)	1.87	0.07
Stage 2 (%)	74.90 (2.65)	76.76 (1.78)	−0.58	0.56
SWS (%)	0.14 (0.07)	0.95 (0.37)	**−2.11**	**0.04**
REM (%)	13.58 (2.54)	15.93 (1.28)	−0.83	0.41
WASO (min)	86.38 (11.37)	83.86 (8.24)	0.18	0.86
Awakenings (#)	17.25 (3.05)	20.30 (1.81)	−0.86	0.4
Arousals (#)	35.70 (7.41)	32.25 (6.09)	0.36	0.72
TST (min)	260.67 (18.74)	300.12 (14.88)	−1.65	0.11
TBT (min)	389.07 (16.79)	397.18 (11.97)	−0.39	0.70
SEI % (TST/TBT)	66.74 (3.66)	75.23 (2.68)	−1.87	0.07

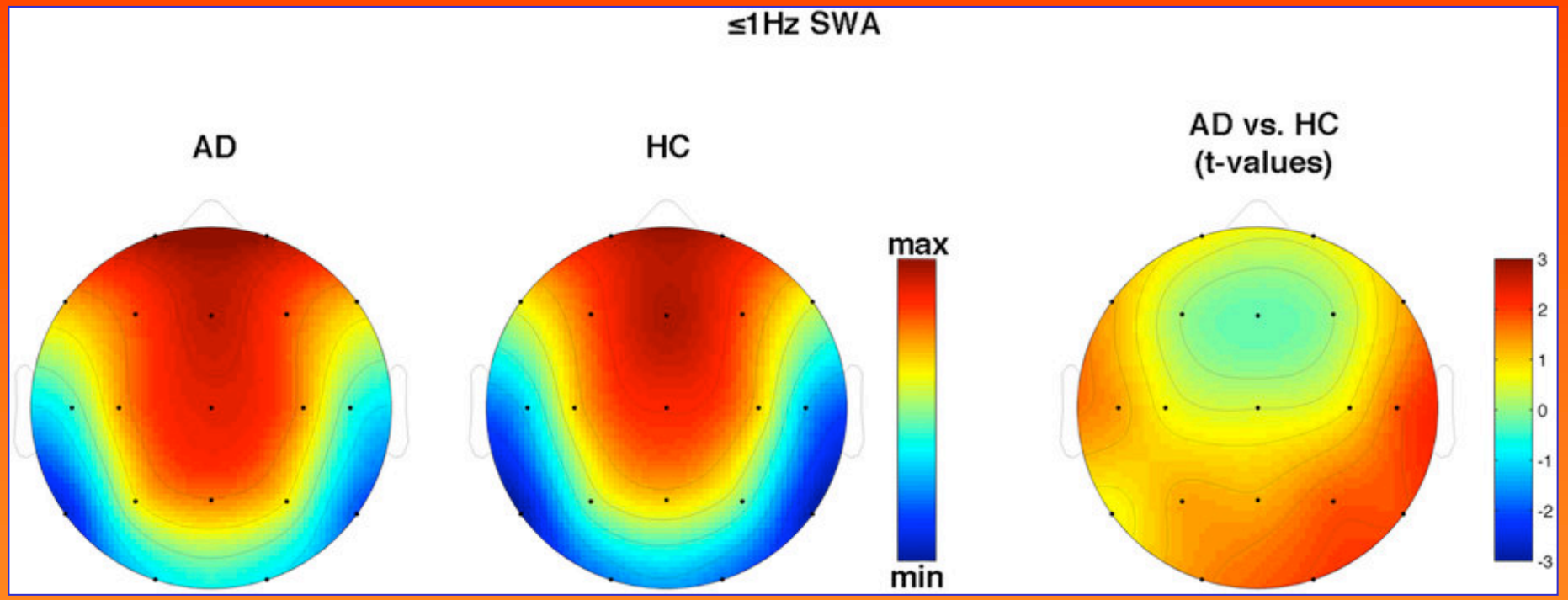


Complessi K nel sonno (KC)

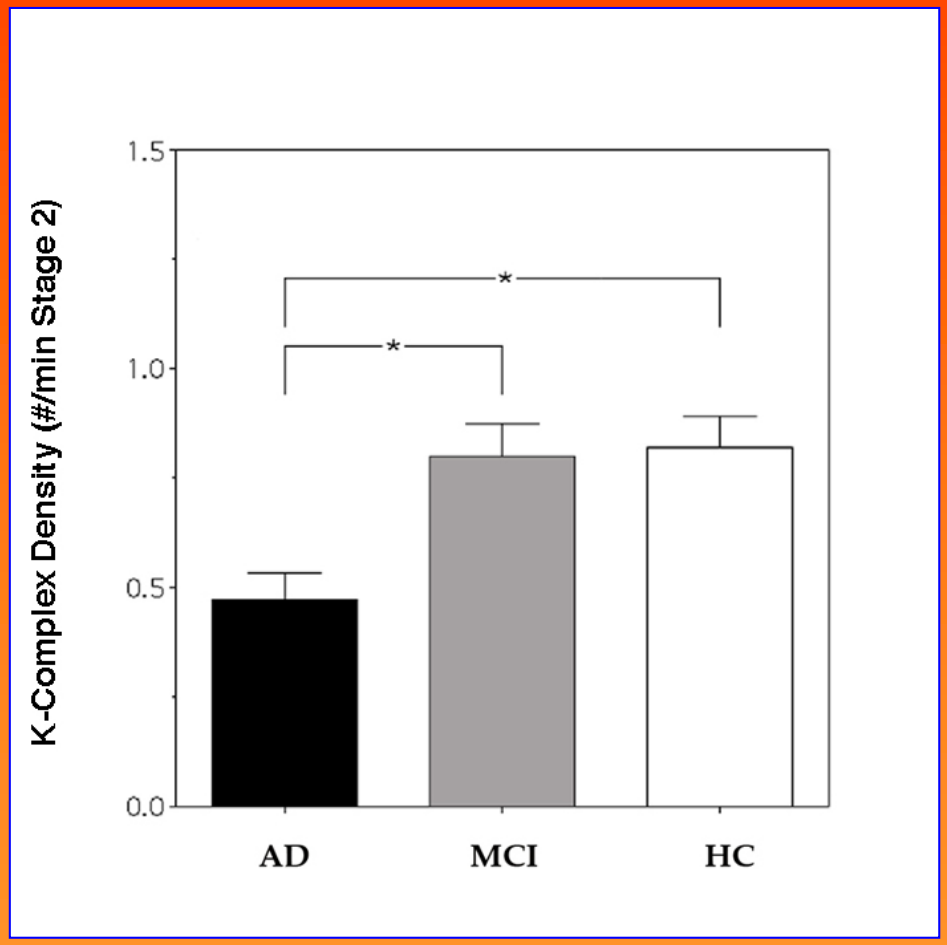




Più del 40% di riduzione dei KCs in pazienti Alzheimer *vs*. controlli



Le oscillazioni lente durante il sonno sono effettivamente minori nei pazienti Alzheimer, ma di dimensioni enormemente meno ampie di quelle stesse dei complessi K. Inoltre, solo il decremento dei complessi K si associa ai punteggi al *Mini Mental State Examination* (MMSE) che misura il decadimento cognitivo

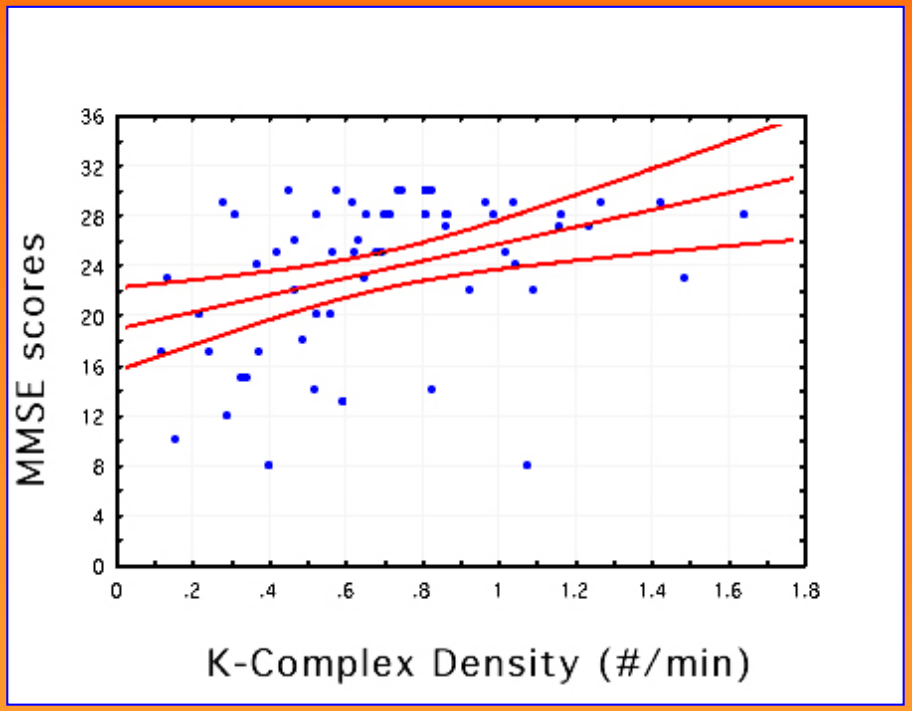


brain sciences

Article

In search of sleep biomarkers of Alzheimer's disease: K-complexes do not discriminate between patients with mild cognitive impairment and healthy controls

Flaminia Reda[1], Maurizio Gorgoni [1], Giulia Lauri[1], Ilaria Truglia[1], Susanna Cordone[1], Serena Scarpelli[1], Anastasia Mangiaruga[1], Aurora D'Atri[1], Michele Ferrara[2], Giordano Lacidogna[3], Camillo Marra[3], Paolo Maria Rossini[3,4] and Luigi De Gennaro[1,*]



… ma i complessi K non discriminano MCI *da* controlli

Hindawi Publishing Corporation
Neural Plasticity
Volume 2016, Article ID 8376108, 10 pages
http://dx.doi.org/10.1155/2016/8376108

Hindawi

Research Article

Parietal Fast Sleep Spindle Density Decrease in Alzheimer's Disease and Amnesic Mild Cognitive Impairment

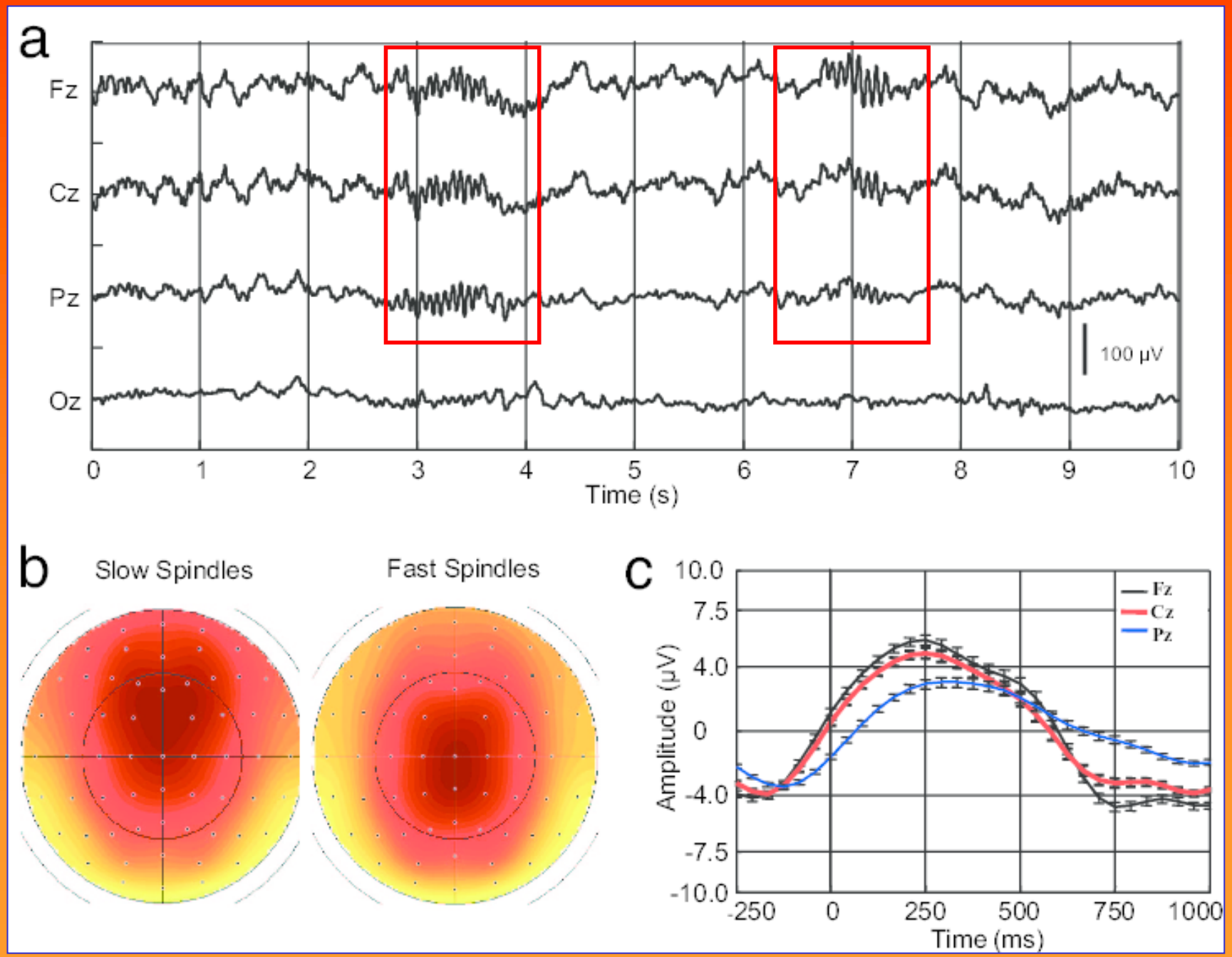
Maurizio Gorgoni,[1] Giulia Lauri,[1] Ilaria Truglia,[1] Susanna Cordone,[2] Simone Sarasso,[3] Serena Scarpelli,[1] Anastasia Mangiaruga,[1] Aurora D'Atri,[1] Daniela Tempesta,[4] Michele Ferrara,[5] Camillo Marra,[6] Paolo Maria Rossini,[6,7] and Luigi De Gennaro[1]

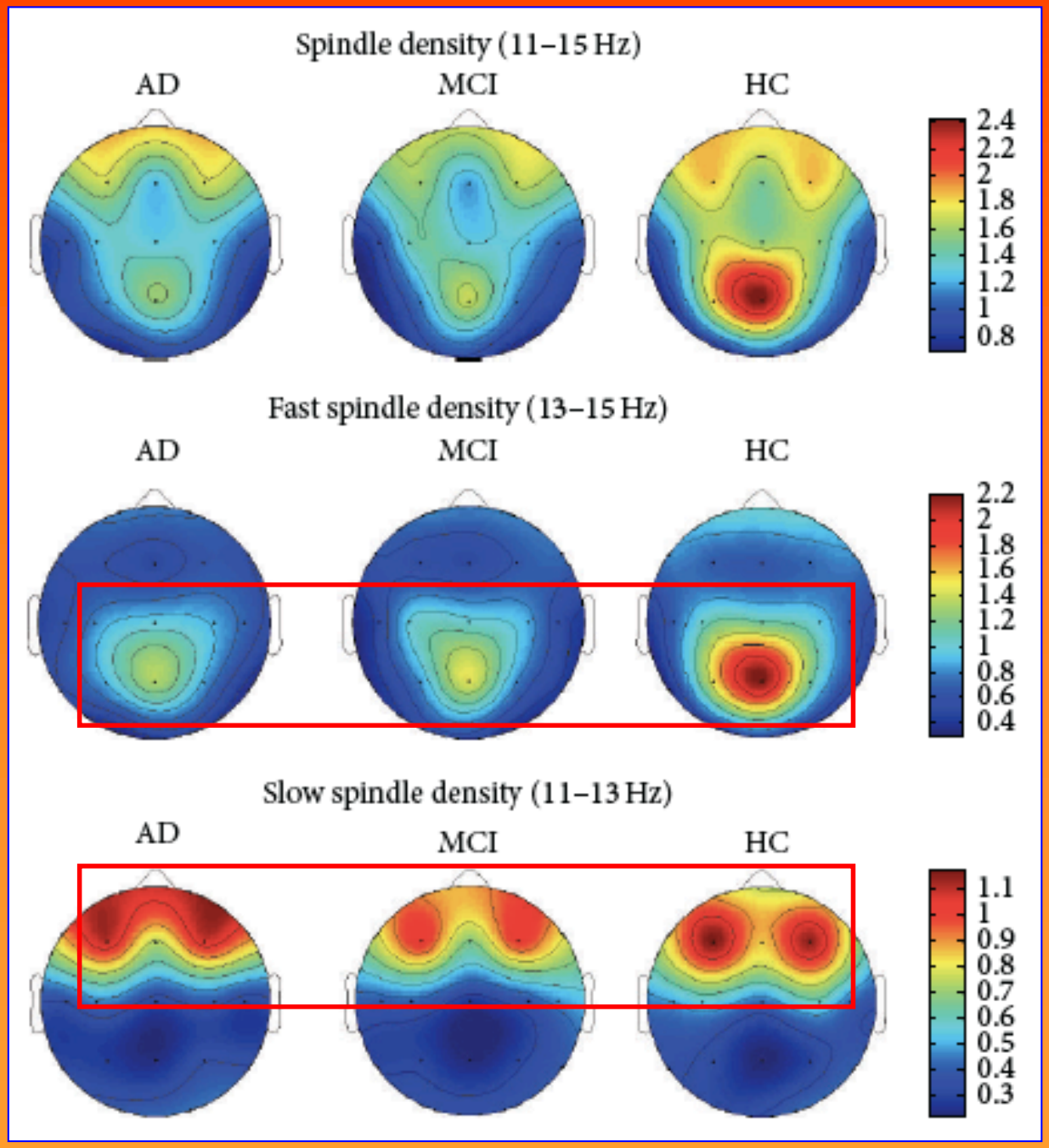
TABLE 2: Mean and standard errors of the polysomnographic variables of AD patients, amnesic MCI patients, and HC. The results of the one-way ANOVAs (F and p values) were also reported, with *post hoc* unpaired t-test (p values) when ANOVAs were significant ($p \leq 0.05$). Significant between-groups differences are indicated in bold.

Variables	AD Mean (SE)	MCI Mean (SE)	HC Mean (SE)	$F_{2,42}$	p	AD versus MCI	AD versus HC	MCI versus HC
Stage 1 latency (min)	41.04 (9.78)	27.44 (4.88)	19.58 (5.86)	2.30	0.11	—	—	—
Stage 2 latency (min)	33.27 (8.61)	26.61 (4.32)	13.29 (4.58)	2.73	0.08	—	—	—
Stage 1 (%)	13.33 (3.06)	9.34 (1.44)	6.55 (1.33)	2.63	0.08	—	—	—
Stage 2 (%)	75.92 (3.33)	76.21 (1.88)	77.91 (2.10)	0.18	0.83	—	—	—
SWS (%)	0.08 (0.05)	0.14 (0.08)	0.79 (0.34)	**3.73**	**0.03**	0.53	**0.05**	0.07
REM (%)	10.66 (2.78)	14.28 (1.85)	15.22 (1.53)	1.29	0.28	—	—	—
WASO (min)	92.24 (14.25)	100.89 (14.06)	90.37 (8.98)	0.20	0.82	—	—	—
Awakenings (#)	18.13 (3.87)	21.33 (2.13)	20.13 (2.23)	0.32	0.73	—	—	—
Arousals (#)	40.00 (9.53)	32.73 (6.53)	34.40 (7.96)	0.22	0.80	—	—	—
TST (min)	263.82 (22.46)	274.31 (16.02)	303.36 (17.22)	1.19	0.31	—	—	—
TBT (min)	388.09 (20.91)	401.47 (9.60)	406.82 (13.52)	0.39	0.68	—	—	—
SEI% (TST/TBT)	67.56 (4.15)	68.31 (3.61)	74.13 (2.98)	0.99	0.38	—	—	—

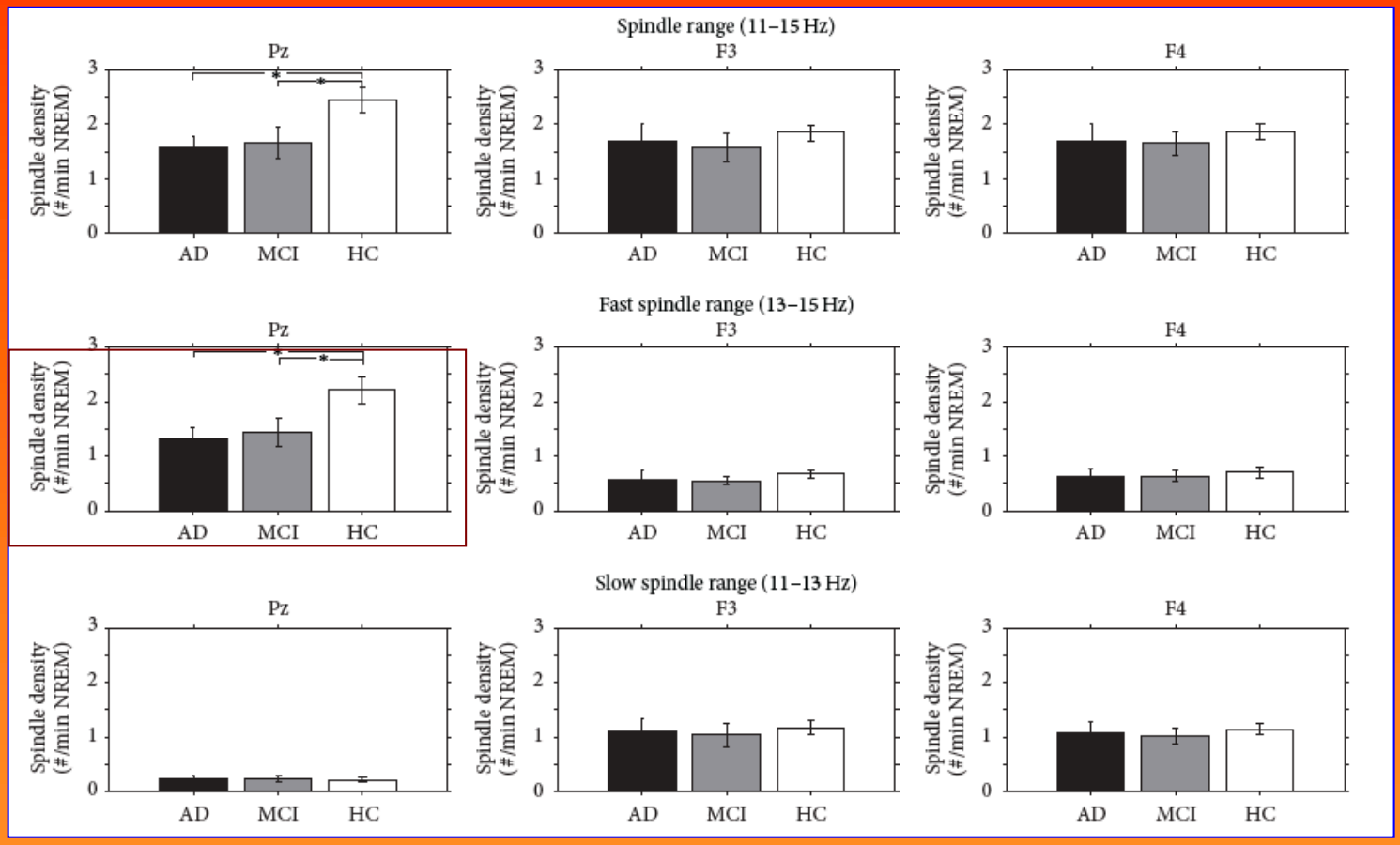
SWS, slow-wave sleep; REM, rapid eye movement; WASO, waking after sleep onset; TST, total sleep time; TBT, total bed time; SEI, sleep efficiency index.

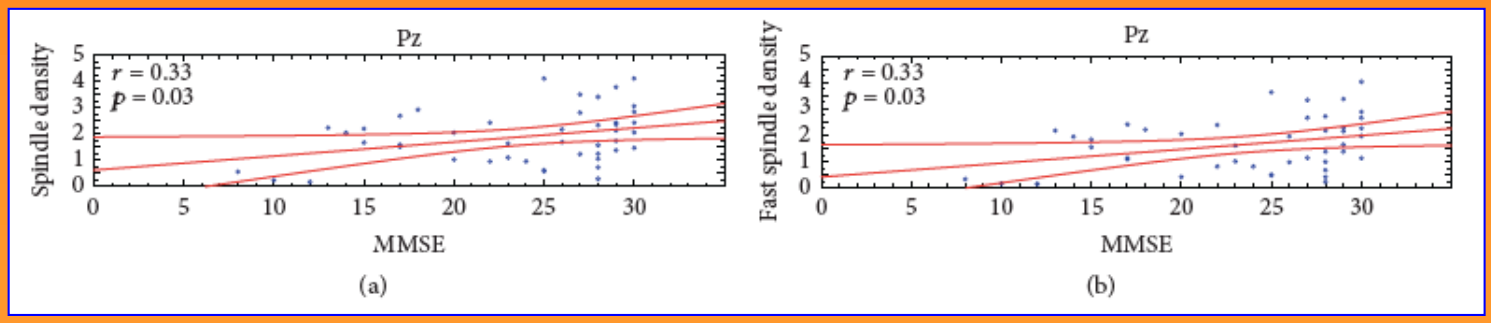
- **Differenze nella macrostruttura del sonno meno ampie di quanto riportato**
- **Diminuzione dello *Slow-Wave Sleep* (SWS) in AD e MCI, rispetto a controlli**


a
Fz
Cz
Pz
Oz
100 µV
0
1
2
3
4
5
6
7
8
9
10
Time (s)
b
Slow Spindles
Fast Spindles
c
10.0
7.5
4.0
0
-4.0
-7.5
-10.0
Amplitude (µV)
Fz
Cz
Pz
-250
0
250
500
750
1000
Time (ms)



Chiara dissociazione tra *spindles* a bassa e alta frequenza
Solo i più rapidi chiaramente discriminano i gruppi clinici dai controlli





Il decremento dei fusi rapidi si associa ai punteggi al MMSE che misura il decadimento cognitivo

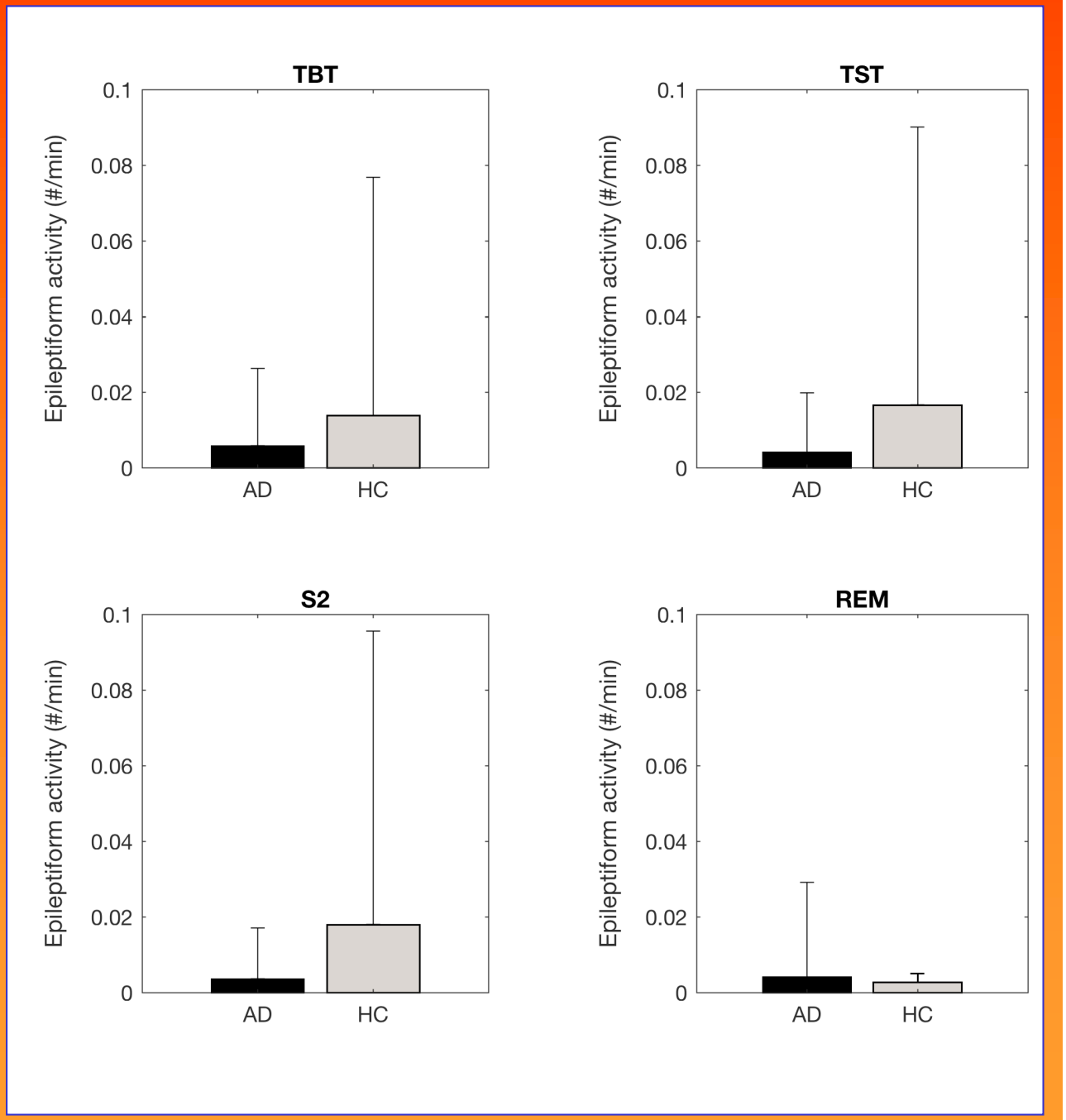
A volte, la ricerca prende strade sbagliate

Incidence and Impact of Subclinical Epileptiform Activity in Alzheimer's Disease

Keith A. Vossel, MD, MSc,[1,2] Kamalini G. Ranasinghe, MBBS, PhD,[1] Alexander J. Beagle, BA,[1] Danielle Mizuiri, BS,[3] Susanne M. Honma, BS,[3] Anne F. Dowling, MS,[3] Sonja M. Darwish, MS,[1] Victoria Van Berlo, BS,[4] Deborah E. Barnes, PhD,[5,6] Mary Mantle, REEG/EPT,[3,7] Anna M. Karydas, BA,[1] Giovanni Coppola, MD,[4] Erik D. Roberson, MD, PhD,[8] Bruce L. Miller, MD,[1] Paul A. Garcia, MD,[7] Heidi E. Kirsch, MD, MS,[3,7] Lennart Mucke, MD,[1,2] and Srikantan S. Nagarajan, PhD[3]

Non esiste alcuna differenza tra la frequenza subclinica di punte epilettiformi di pazienti Alzheimer e anziani di controllo

(***Annals of Neurology, in revision***)



Il più grande progetto di ricerca mai eseguito sul sonno dei malati di Alzheimer e sugli MCI

SAPIENZA
UNIVERSITÀ DI ROMA

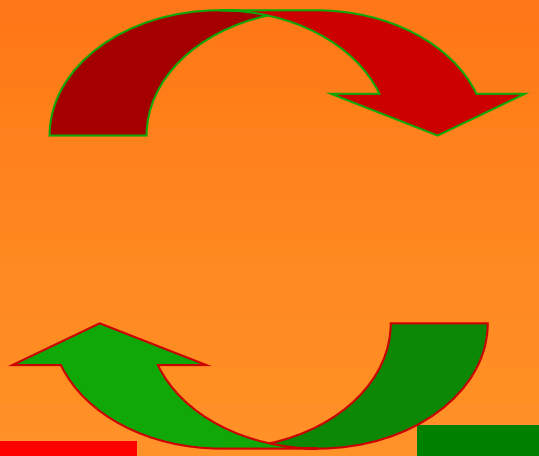
Gemelli
Fondazione Policlinico Universitario A. Gemelli
Università Cattolica del Sacro Cuore

UNIVERSITÀ DEGLI STUDI
DELL'AQUILA

INCREMENTO FREQUENZE EEG LENTE
Delta
Theta

SLOWING EEG durante la veglia

DECREMENTO FREQUENZE EEG RAPIDE
Alpha
Beta



Sonno

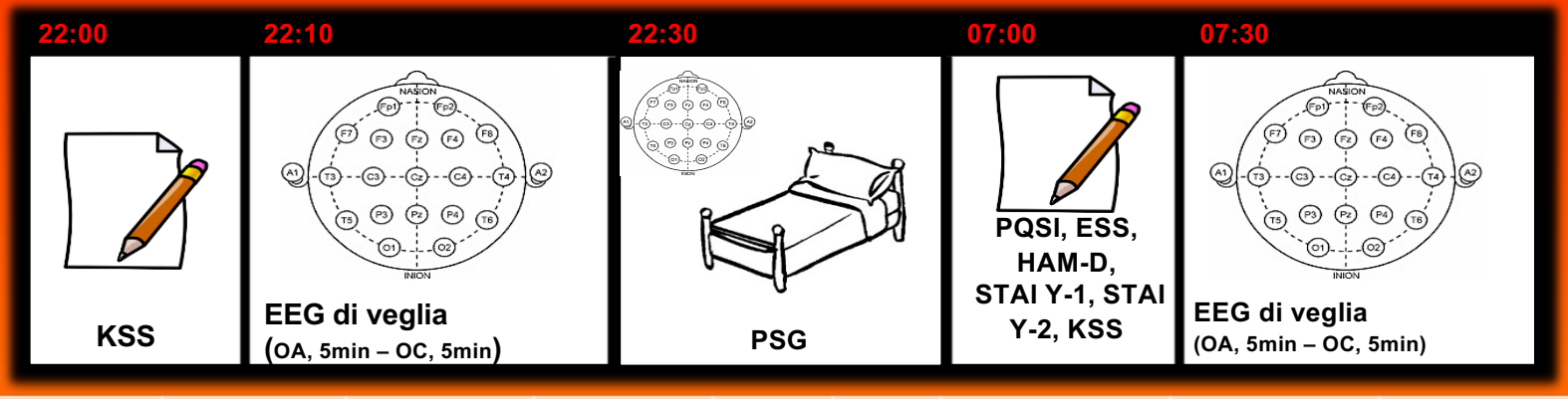
Aumento stadio 1

- Riduzione *Slow Wave Activity* (SWA)
- Declino durata REM
- *Slowing* EEG fase REM

Veglia

- *Slowing* EEG

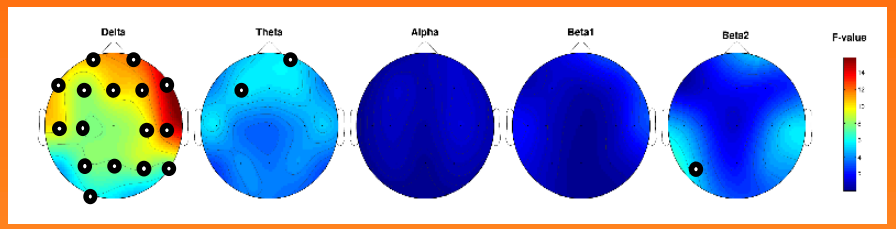
(incremento frequenze lente più marcato in aree posteriori)

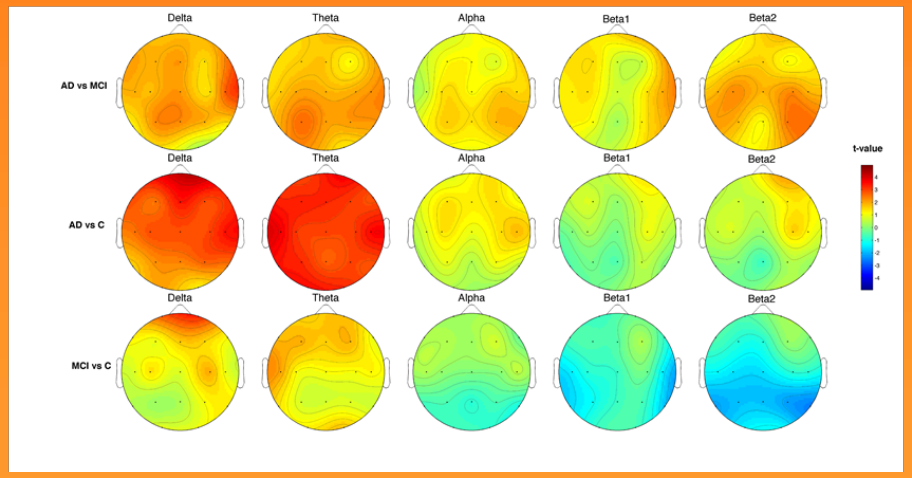


Variables	AD		MCI		Ctrl.		F	P	AD vs MCI		AD vs CONTROLS		MCI vs CONTROLS	
	Media	d.s.	Media	d.s.	Media	d.s.			t	p	t	p	T	P
Stage 1 latency	38.38	45.17	25.08	20.57	24.47	20.50	2.619	.07	1.870	.06	1.781	.07	0.119	.90
Stage 2 latency	38.70	44.91	23.77	17.89	16.53	16.34	7.188	.001	2.160	.03	3.251	.002	2.112	.03
Stage 3 latency	123.38	95.90	103.65	74.52	62.90	45.72	4.322	.01	0.602	-55	2.813	.007	2.292	.02
REM latency	114.41	85.18	116.57	85.88	108.78	62.96	0.128	.87	-0.117	.90	0.356	.72	0.511	.60
Stage 1	26.08	23.36	24.76	19.86	18.77	14.24	2.247	.10	0.295	.76	1.974	.05	1.874	.06
Stage 2	198.58	60.91	208.65	60.59	220.01	50.33	1.627	.20	-0.797	.42	-1.858	.06	-1.020	.31
Stage 3	0.64	2.41	0.41	0.78	2.02	3.56	5.186	.006	0.597	-55	-1.978	.05	-2.933	.004
NREM	199.10	60.79	208.68	60.91	222.14	50.85	1.890	.15	-0.756	.45	-1.989	.05	-1.199	.23
REM	46.55	35.65	46.65	22.31	47.22	21.38	0.008	.99	-0.016	.98	-0.111	.91	-0.131	.89
Stage 1 (%)	10	10	7.8	5.6	6.5	5.7	2.501	.08	1.245	.21	2.026	.04	1.097	.27
Stage 2 (%)	74	10.4	74.1	10.2	76.8	6.6	1.443	.23	-0.010	.99	-1.542	.12	-1.572	.11
Stage 3 (%)	0.2	10	0.1	0.2	1.3	2.6	5.840	.003	0.960	.34	-2.084	.04	-2.840	.005
NREM (%)	74.3	10.4	74.31	14.2	70.8	7	1.982	.30	-1.361	.17	-2.034	.04	1.453	.14
REM (%)	16.1	9.9	17.8	8.4	15.1	5.9	1.364	.25	-0.872	.35	0.605	.54	1.841	.06
WASO (min)	84.8776.8	50.49	89.86	50.71	81.28	48.48	0.373	.68	-0.474	.63	0.349	.72	0.865	.38
Movement Arousal (MA)	35.81	37.50	34.32	31.17	30.54	30.73	0.321	.72	0.209	.83	0.745	.45	0.610	.54
TST	273.75	76.85	282.11	65.99	287.65	59.52	0.484	.61	-0.548	.58	-0.971	.33	0.430	.66
TBT	392.37	57.65	416.28	92.69	384.93	44.88	2.825	.06	-1.465	.14	0.698	.48	2.152	.03
SEI (%)	69.2	15.1	69.8	16.5	74.3	14.1	1.561	.21	-0.193	.61	-0.66	.50	-1.15	.25

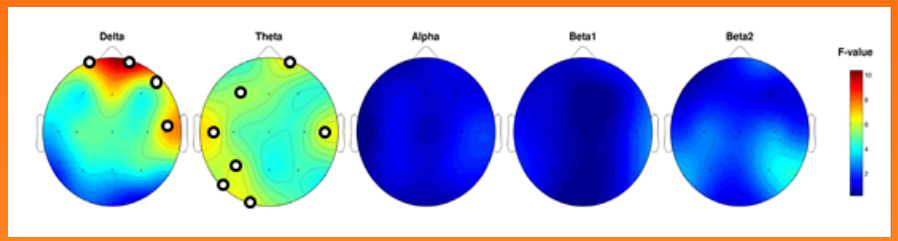
Veglia (OA) in diversa fase circadiana

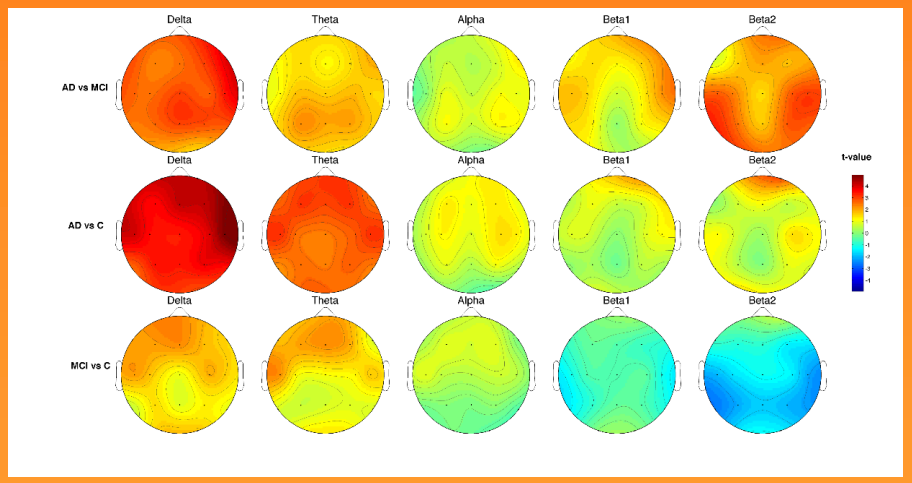
9.00 p.m.





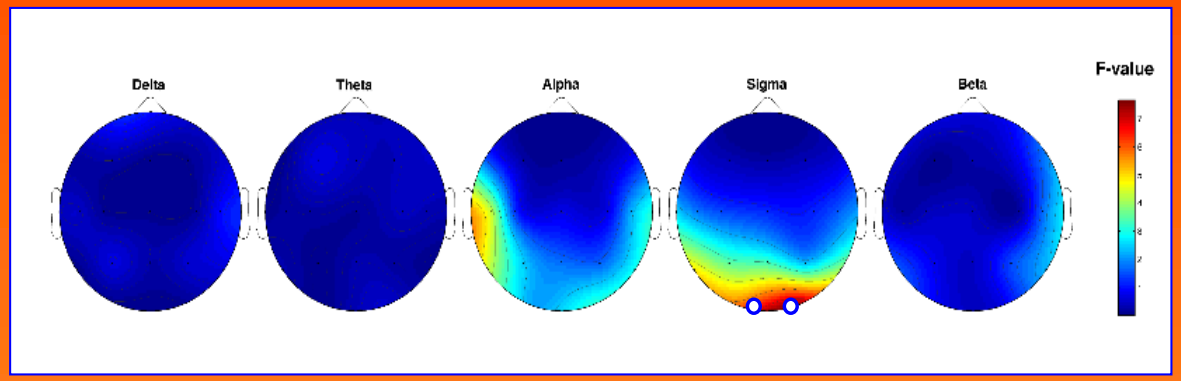
9 a.m.

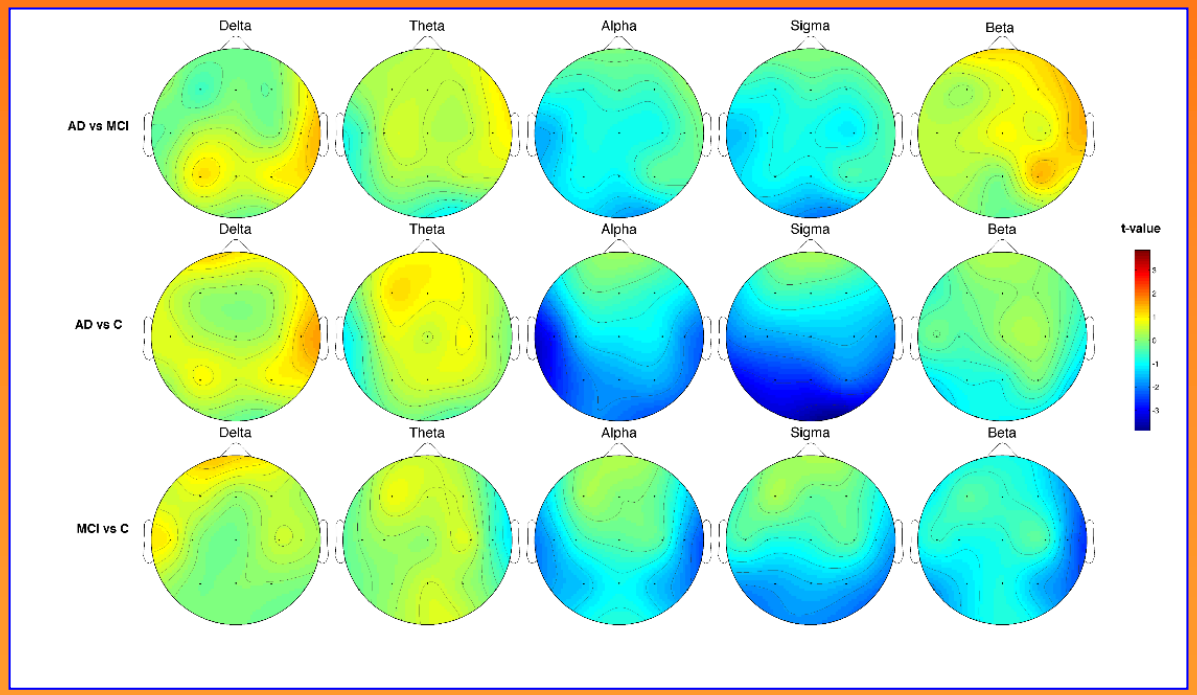




- **Specificità regionale del fenomeno dello *slowing* EEG**
- **Relativa indipendenza da modulazioni circadiane**

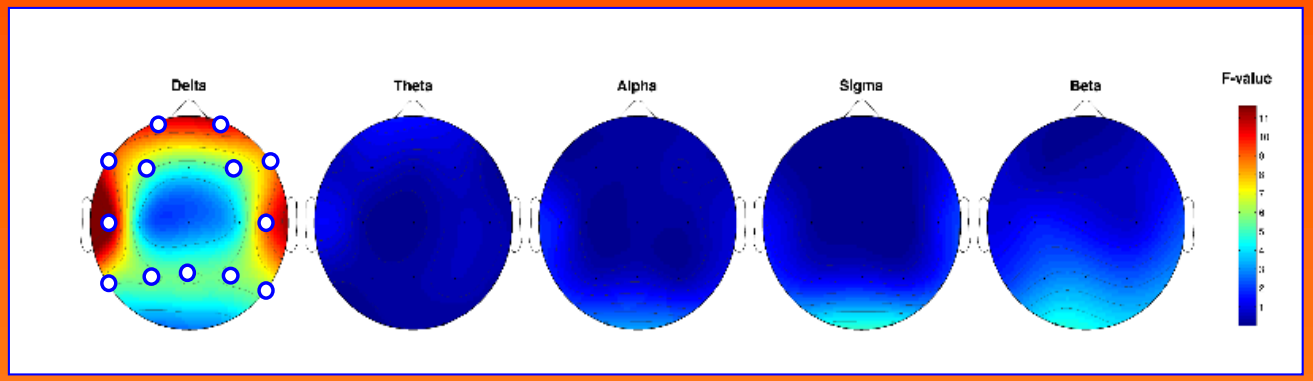
Sonno NREM

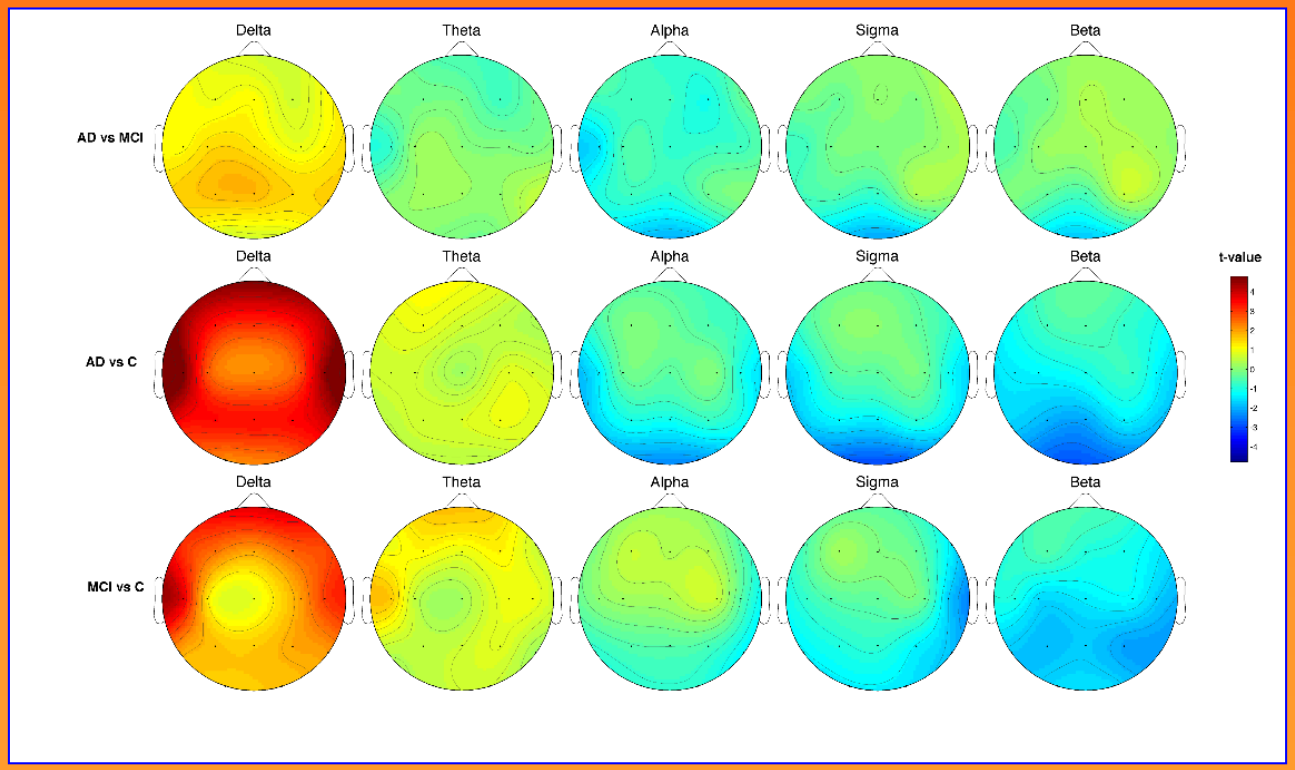




- **Diminuzione occipitale di *sigma activity* (*spindles*) in AD**

Sonno REM

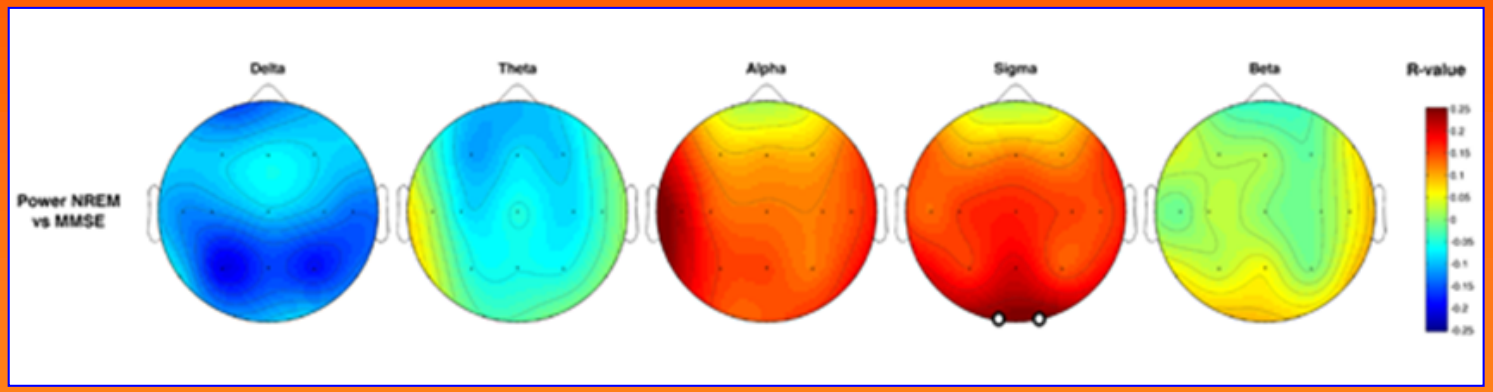




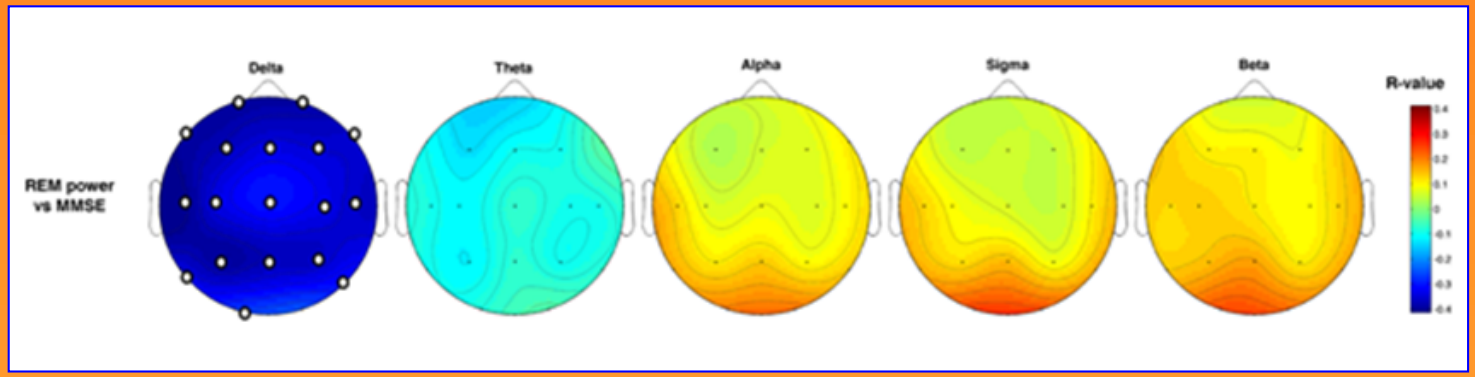
- **Esteso incremento di attività lenta (*slowing*) in AD e MCI**

Relazione tra EEG power e MMSE

NREM



REM



- **Associazione topograficamente specifica tra entità delle differenze di attività EEG e declino cognitivo (MMSE)**

T0

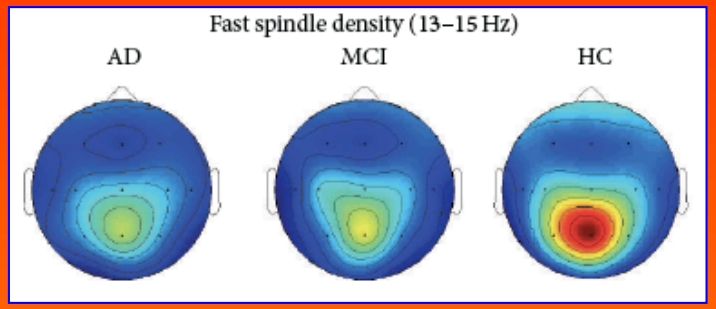
T1 (almeno 1 anno dopo)

MCI = 50

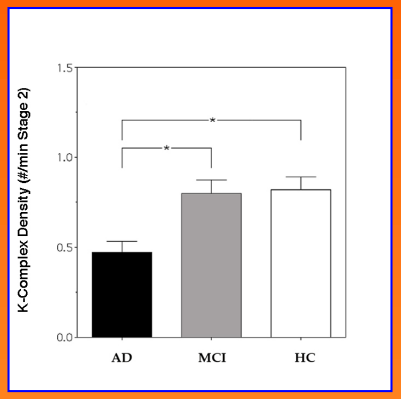
AD converted

AD non-converted

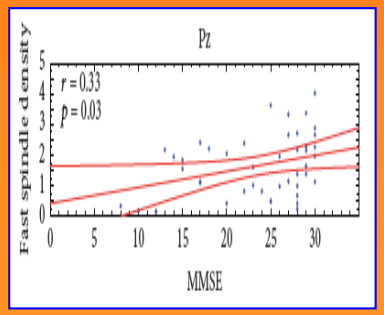
L'elettrofisiologia (diurna e notturna) degli MCI predice la conversione in Alzheimer?

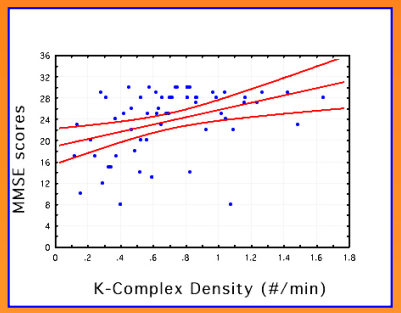


- I fusi del sonno a frequenza più rapida su aree parietali appaiono precocemente le prime fasi della malattia



- I complessi K frontali, pur essendo drasticamente ridotti in AD, non sono *marker* precoci



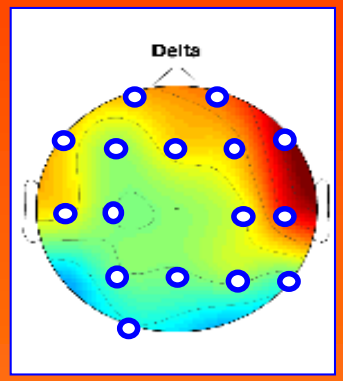


- Variazioni degli eventi fasici del NREM sono correlate all'entità del deficit al MMSE

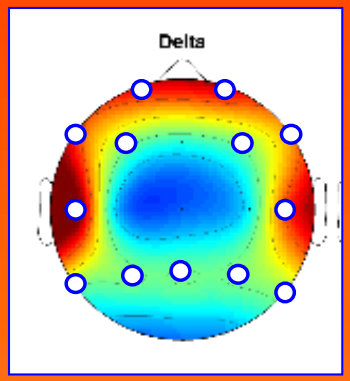
Latenza Stadio 2 ↑
Latenza Stadio 3 ↑
% Stadio 3 ↓

- < alterazioni della macrostruttura del sonno di quanto descritto

Veglia

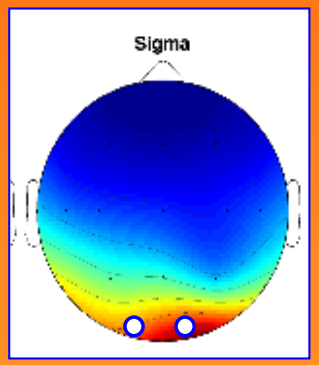


Sonno

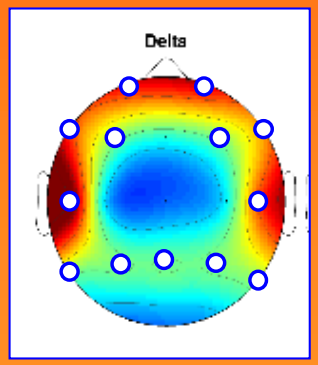


- **Tra le due ipotesi alternative a confronto sembra suffragata quella di comuni meccanismi anatomo-fisiologici (tra veglia e sonno)**

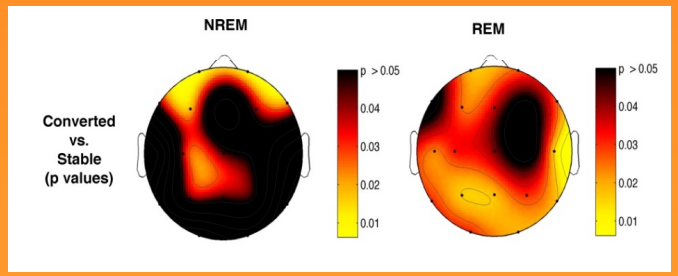
NREM



REM



- **Alterazioni regionali dell'EEG più marcate in sonno REM (*slowing*)**



- **Un quadro EEG di maggiori frequenze lente appare predittivo di futura conversione negli MCI**

E l'integrazione con il Sant'Andrea?

EDITION IT

HUFFPOST
IN COLLABORAZIONE CON GEDI

POLITICA ECONOMIA ESTERI CULTURE CITTADINI BLOG VIDEO ALTRO

Luigi De Gennaro
Psicofisiologo, esperto di disturbi del sonno

IL BLOG

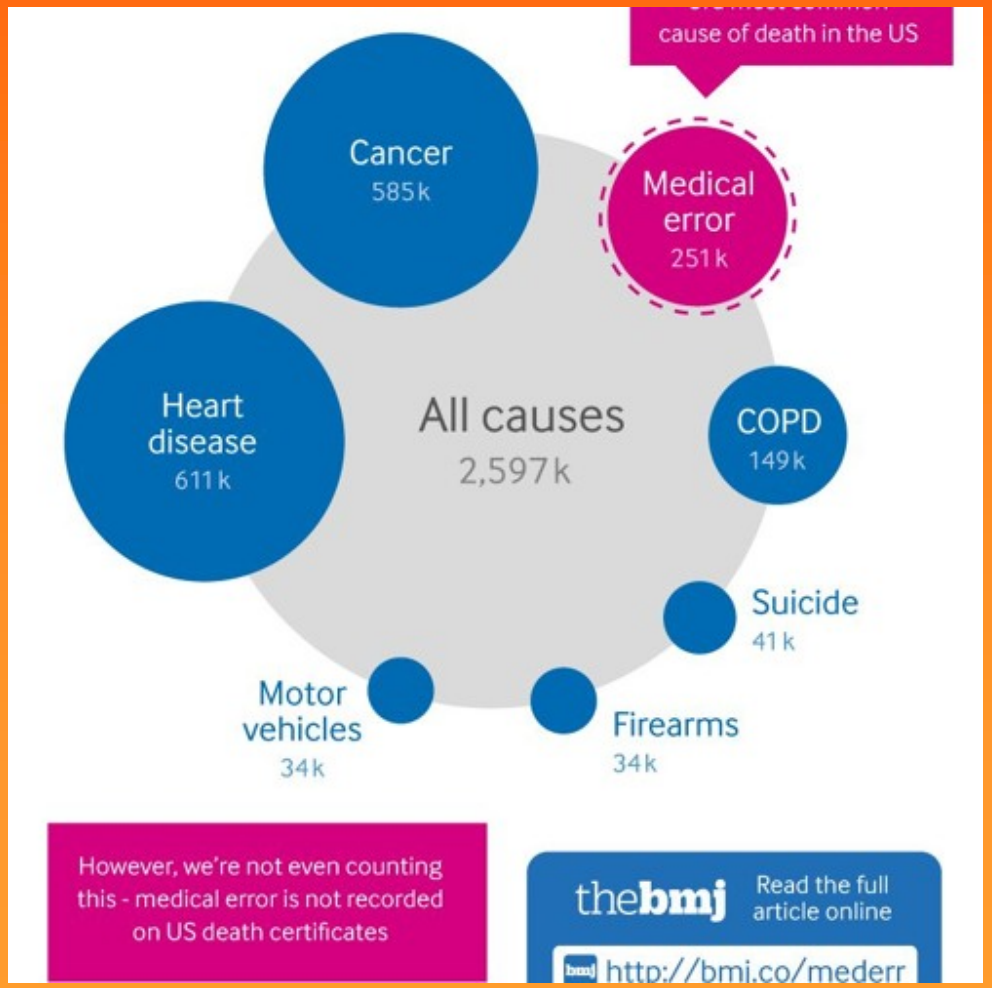
Errori medici terza causa di morte negli Usa. Una riflessione sul lavoro notturno

06/01/2019 18:41 CET | Aggiornato 09/01/2019 11:17 CET

TENDENZE


Federico Pizzarotti: "Qui salta tutto, stiamo pronti"


"Negli anni 80 e 90 i soldi non finivano mai. Era difficile evitare la cocaina a Milano: tutto tempo perso"



Journal of *Clinical Medicine*

I.F= 5.583

MDPI

Article

Not only a Problem of Fatigue and Sleepiness: Changes in Psychomotor Performance in Italian Nurses across 8-h Rapidly Rotating Shifts

Marco Di Muzio [1], Flaminia Reda [2], Giulia Diella [1], Emanuele Di Simone [3], Luana Novelli [2], Aurora D'Atri [2], Annamaria Giannini [2] and Luigi De Gennaro [2,*]

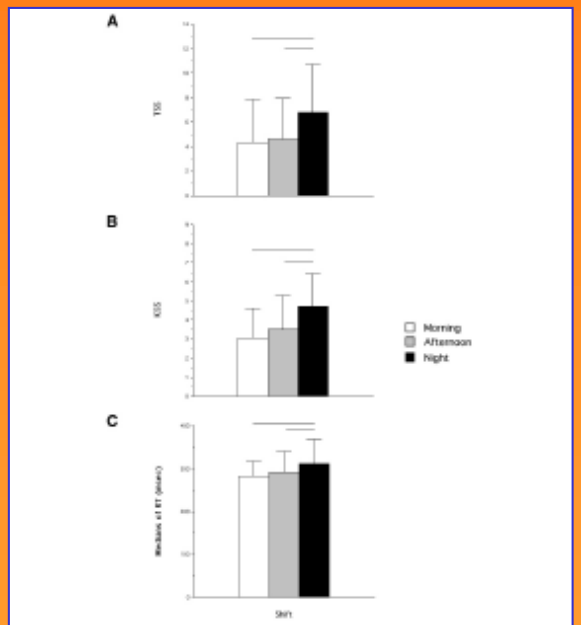


Figure 1. Means and standard deviations of the dependent variables measures in the sample of Italian nurses collected across different rapidly rotating shifts (morning, afternoon, and night). Panel A = scores at the Tiredness Symptoms Scale (TSS), panel B = scores at the Karolinska Sleepiness Scale (KSS), and panel C = medians of Reaction Times (RT) at the Psychomotor Vigilance Task (PVT).