Ipotesi colinergica del sonno: tra memoria e comportamento

Luigi Ferini-Strambi

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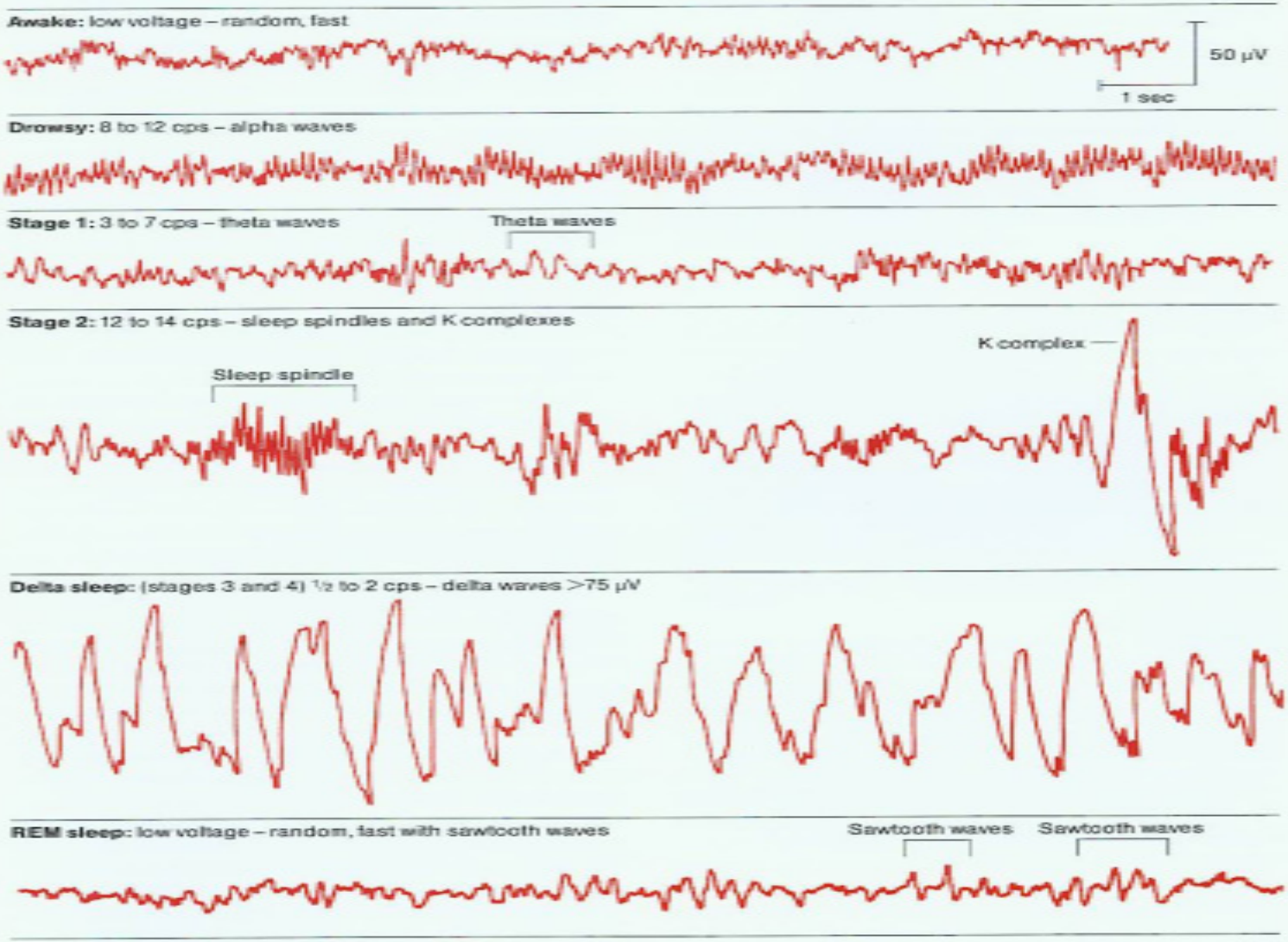
Figure 1
Characteristic electroencephalographic patterns of human sleep stages



Pre - sleep - W

SWS

REM - sleep

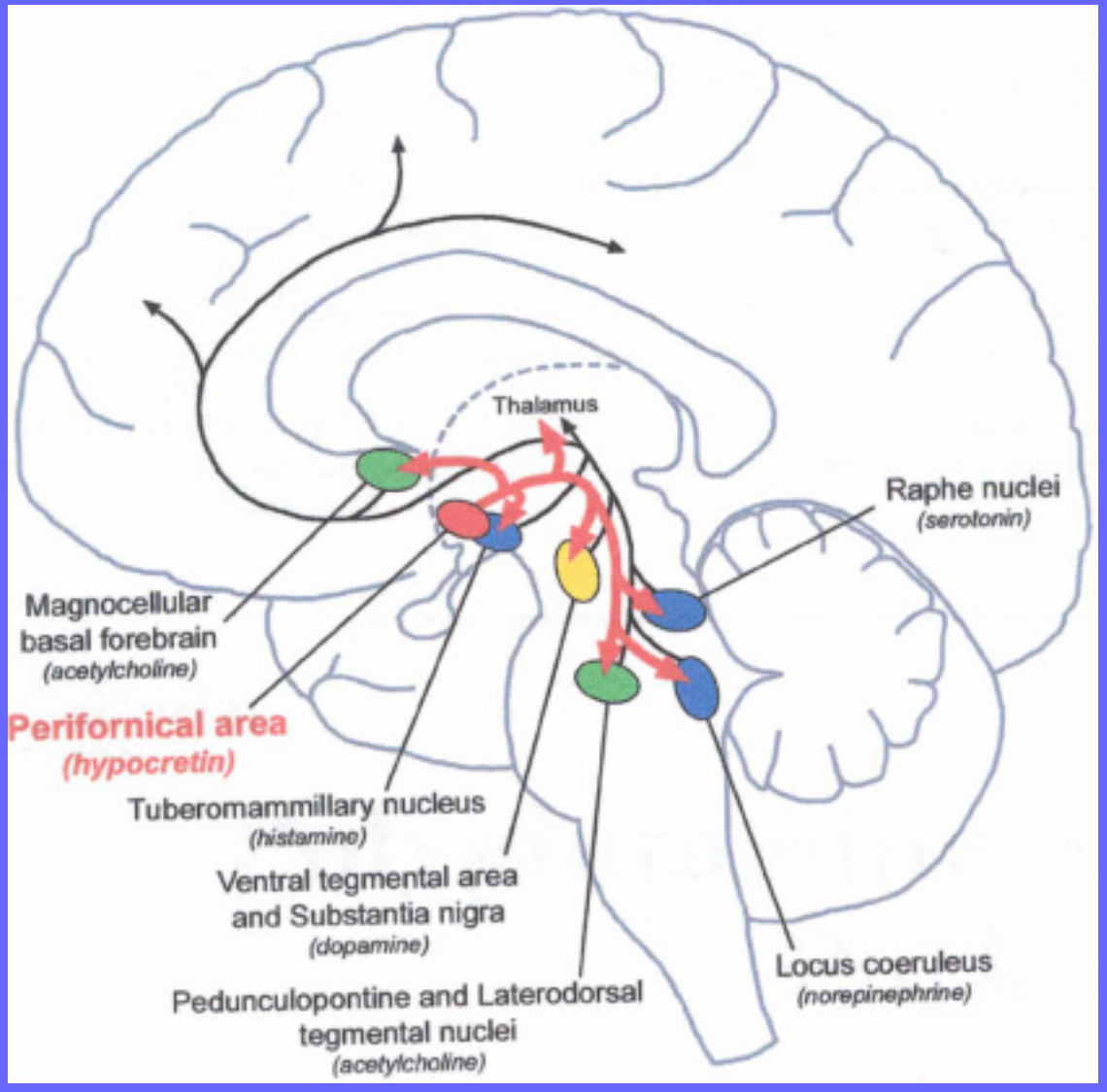
Post - sleep - W

ACTIVATION

High DEACTIVATION

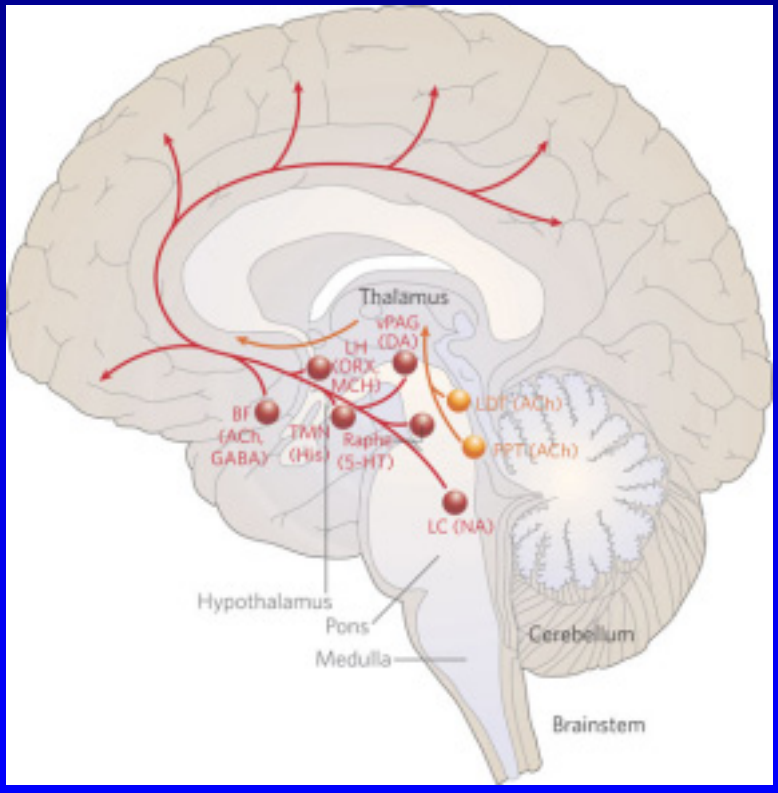
Low DEACTIVATION

BRAUN et al; Brain (1997)

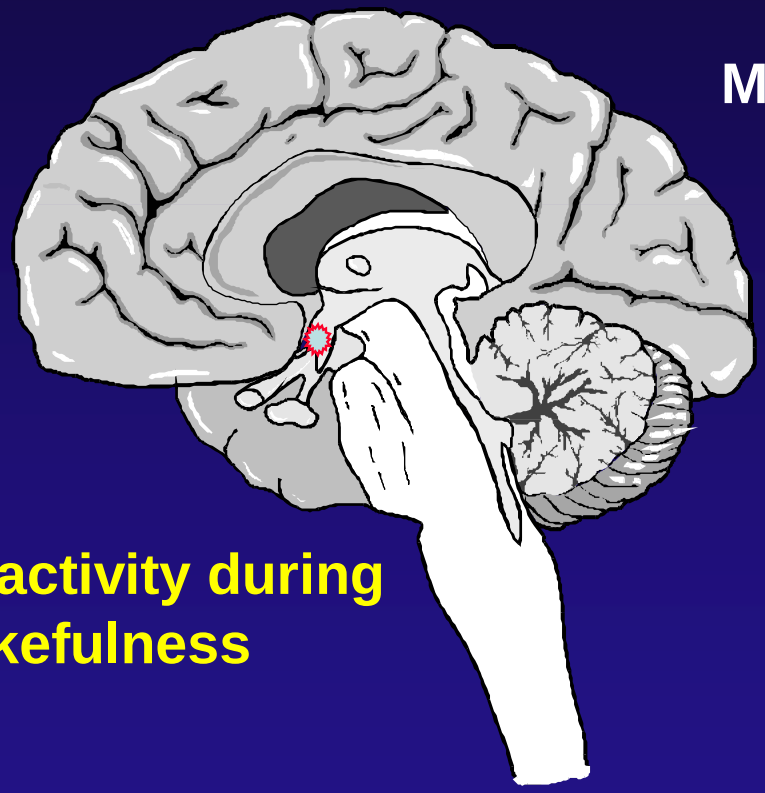

Thalamus
Raphe nuclei
(serotonin)
Magnocellular
basal forebrain
(acetylcholine)
Perifornical area
(hypocretin)
Tuberomammillary nucleus
(histamine)
Ventral tegmental area
and Substantia nigra
(dopamine)
Pedunculopontine and Laterodorsal
tegmental nuclei
(acetylcholine)
Locus coeruleus
(norepinephrine)

Sleep/Wake regulation

Ascending Arousal System



General CNS cholinergic activity



Minimal activity during SWS

Marked activity during wakefulness

Pace-Schott & Hobson, 2002

Effects of cholinesterase inhibitors on sleep in AD patients

- **Incident insomnia for donepezil**

  7-8% of patients treated by 5 mg, 8-10% of patients treated by 10 mg (***Rogers et al, Arch Intern Med 1998; Burns et al, Dement Geriatr Cogn Disord 1999)***
- **No insomnia with morning dose of donepezil** ***(Jackson et al, Br J Clin Pharmacol 2004)***
- **Sleep is not impaired with rivastigmine and galantamine (*Markowitz et al, Sleep 2003)***

Nightmares in patients with Alzheimer's disease caused by donepezil

Singer M et al
Nervenartz 76: 1127-9, 2005

- *A clear-cut relationship between the occurrence of nightmares and evening dose of donepezil in 8 DAT patients*
- *None of these patients reported nightmares when donepezil was taken in the morning*

Acethylcoline and REM sleep

In humans, Ach-esterase inhibitors (eg **physostigmine**) and selective muscarinic-Ach receptor antagonist (eg **pilocarpine**) shorten REM latency without affecting REM duration or number of REMs

Nissen C et al

Neuropsychopharmacology 31: 1294-1300, 2006

Cholinergic regulation of the central nucleus of the amygdala in rats: effects of local microinjections of cholinomimetics and cholinergic antagonists on arousal and sleep

Sanford LD et al

Neuroscience 141: 2167-2176, 2006

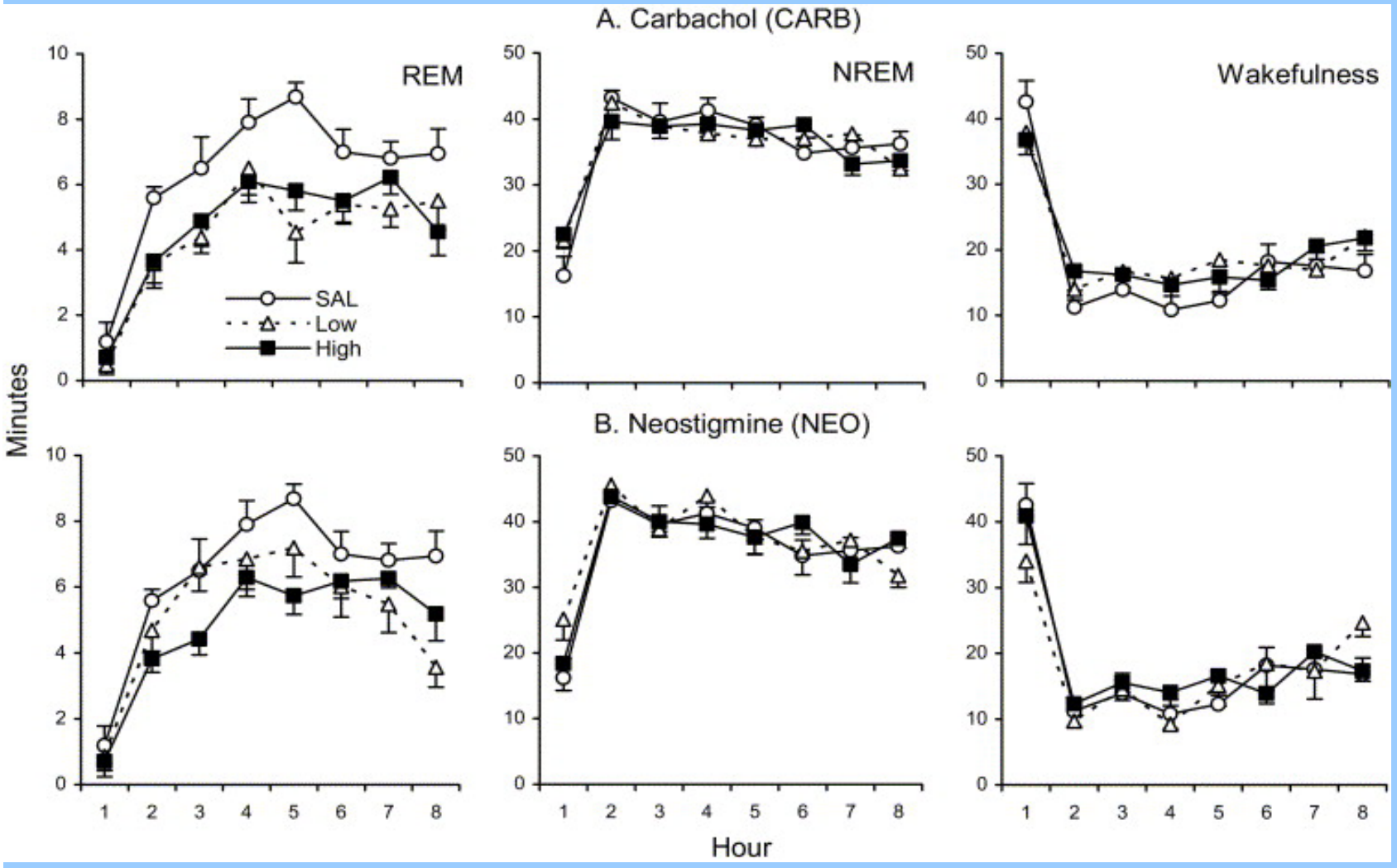


Fig. 2. Hourly plots (means±S.E.M.) of REM, NREM and W time (min) after microinjections of SAL, CARB and NEO into CNA.

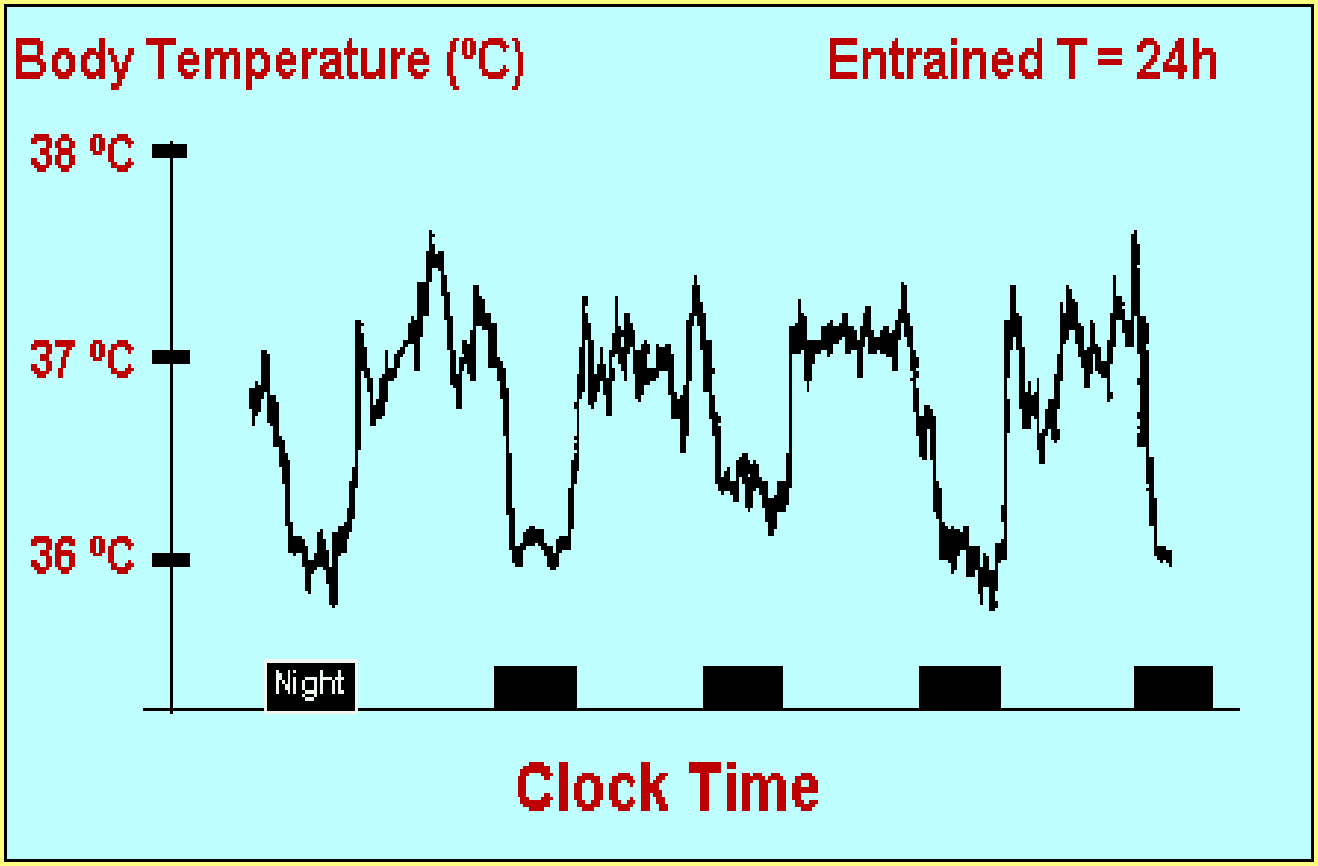
Ach release, EEG spectral analysis, sleep staging and body temperature studies: a multiparametric approach on freely moving rats

Crouzier et al

J Neurosci Methods 151: 159-67, 2006

Waking, body temperature and Ach release present synchronized cycle with close acrophases

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

Ageing Res Rev 2002 Sep;1(4):721

Circadian and age-related modulation of thermoreception and temperature regulation: mechanisms and functional implications.

Van Someren E, Raymann R, Scherder E, Daanen H, Swaab D

At older ages, the circadian rhythm of body temperature shows a decreased amplitude, an advanced phase, and decreased stability.

Passive body heating ameliorates sleep disturbances in patients with vascular dementia without circadian phase-shifting

Mishima Y et al
Am J Geriatr Psychiatry 13: 369-76, 2005

Immersion in hot water about 40° C for 30 min beginning 2 hrs before bedtime

- **Improvement of subjective sleep quality**
- **Reduced sleep latency**
- **Increased sleep efficiency**
- **Increased vagal activity during sleep time**

Difficult Behaviors in Long-term Care Patients With Dementia

Gwendolen T. Bahr, MD, MHSc, and Heidi K. White, MD, MHSc, CMD

J Am Med Dir Assoc 8: 101-113, 2007

Sundown syndrome in AD: conflicting data

- Martin et al (***Chronobiol Int, 2000***): peak of agitation behavior occur closer to 1:00 pm rather than in the evening or at sundown (only 2/90 agitated demented patients peaked at sundown).
- Bliwise et al (***Psychiatry Res, 1993***): no "sundowning" in nursing home patients with dementia.
- Other studies showed that the hours from 4:00 to 8:00 pm are vulnerable to agitation (***O'Leary et al, Psychol Aging 1993; Sloane et al, J Am Geriatr Soc 1998)***
-

However, these results lend support the existence of a circadian rhythm for agitated behaviors in many AD patients

Antipsychotic drug use among nursing home residents taking rivastigmine

Narayanan S et al

J Am Med Dir Assoc 7: 12-6, 2006

Patients in the control group were almost 2 times more likely (rr= 1.86, p<.001) to take antipschotics compared with patients taking rivastigmine, after adjusting for demographic covariates and mental health conditions or behavioral symptoms at baseline.

Sonno REM e M. di Alzheimer

Alcuni cambiamenti della struttura ipnica sono <u>peculiari</u> della MA:

Normali meccanismi di "iniziazione" e normali caratteristiche del sonno REM (popolazioni colinergiche mesopontine risparmiate)

<u>Alterati meccanismi di mantenimento del sonno REM</u> (degenerazione dei neuroni colinergici del N. basale del Meynert = ridotte influenze inibitorie sui nn. reticolari del talamo promotori del sonno NREM = sbilanciamento NREM-REM)

Petit D, Gagnon JF, Fantini ML, Ferini-Strambi L, Montplaisir J.
J Psychosom Res,2004; 56:487

Sleep and quantitative EEG in AD

- **In veglia:**
  - **Rallentamento della frequenza occipitale dominante (alfa theta)**
  - **Aumento dell'attività delta**

- **In sonno REM:**
  - **Rallentamento dell'attività elettrica corticale <u>più marcato</u> che in veglia.**
  - **L'indice di rallentamento EEG in REM nelle regioni <u>temporali</u>: marker con potere discriminante del 90.4 % nel distinguere AD da controllli sani**

<u>Le conseguenze di un deficit colinergico sono molto più evidenti nel sonno REM</u>

Petit D, Gagnon JF, Fantini ML, Ferini-Strambi L, Montplaisir J. J Psychosom Res, 2004

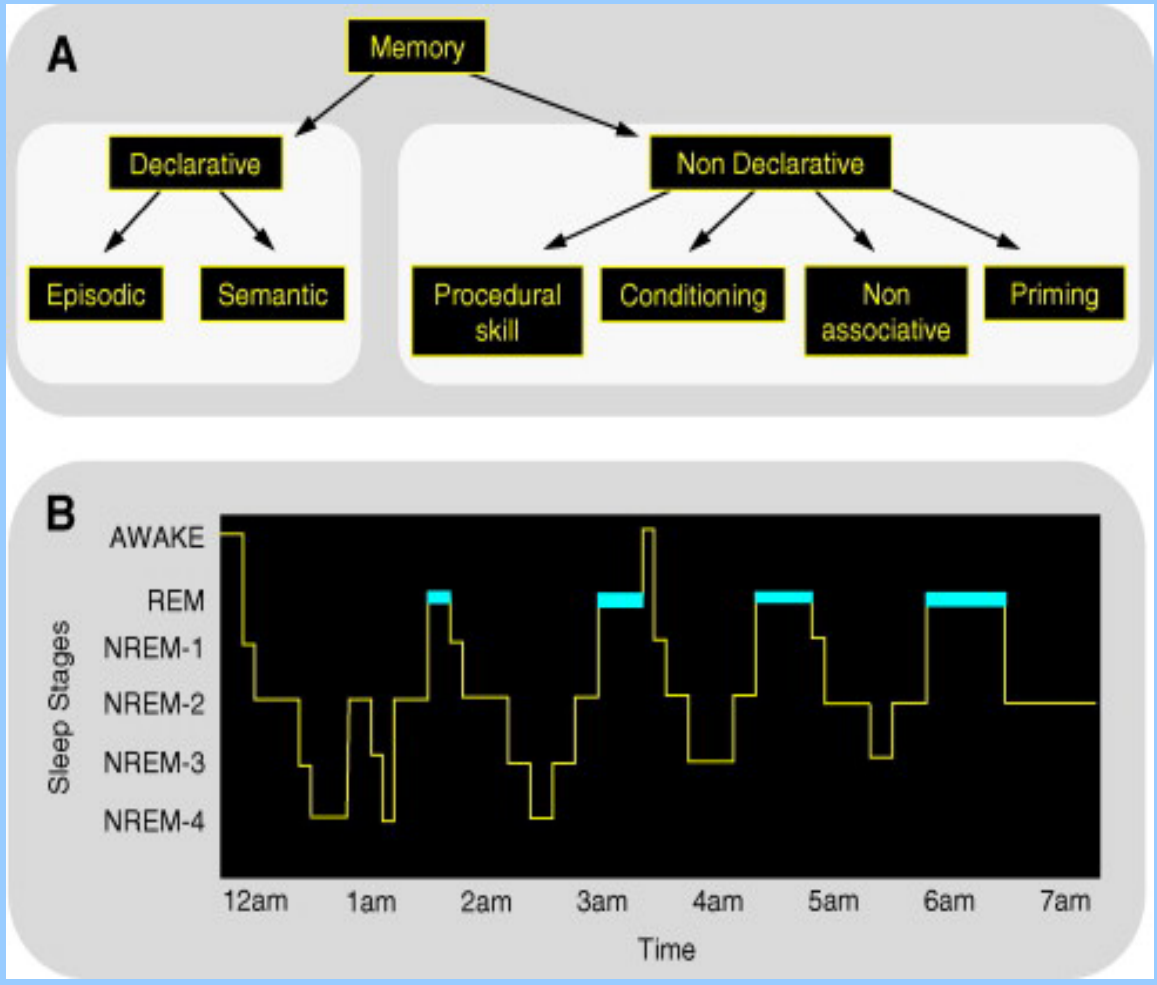
NATURE|Vol 444|30 November 2006

NEUROSCIENCE

A memory boost while you sleep

Robert Stickgold

It is generally agreed that sleep aids memory consolidation, but the reasons for this are a mystery. Part of the answer may lie in the patterns of synchronous brain activity unique to the state of slumber.


A
Memory
Declarative
Non Declarative
Episodic
Semantic
Procedural skill
Conditioning
Non associative
Priming
B
AWAKE
REM
NREM-1
NREM-2
NREM-3
NREM-4
Sleep Stages
12am
1am
2am
3am
4am
5am
6am
7am
Time

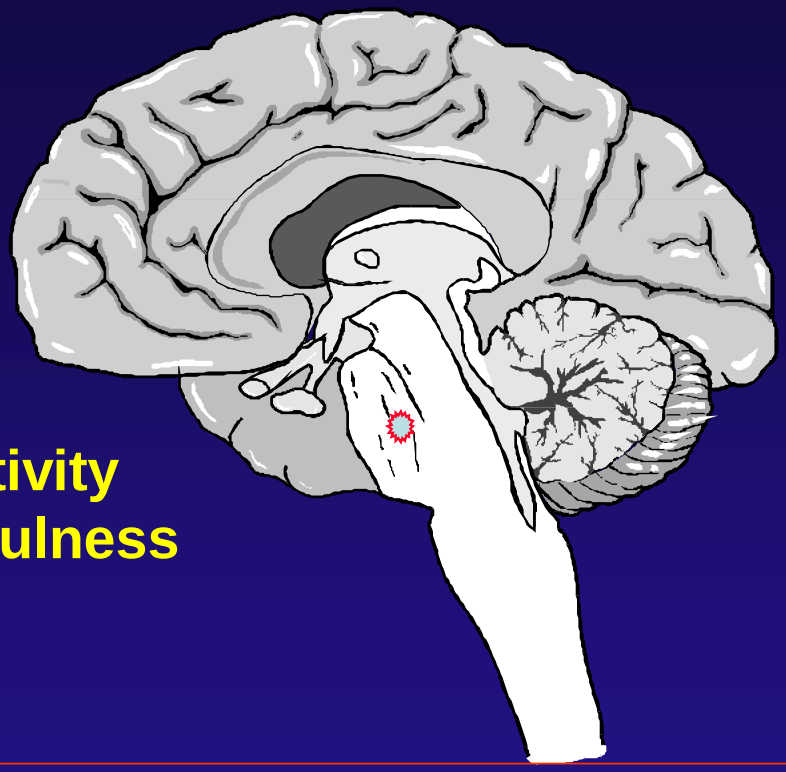
Procedural tasks (usually implicit) require REM sleep for efficient memory consolidation

Non-REM sleep is correlated with the acquisition of the declarative material

Fogel MS et al

Behavior Brain Res 180: 48-61, 2007

CNS cholinergic activity and memory



Minimal activity during SWS

Marked activity during wakefulness

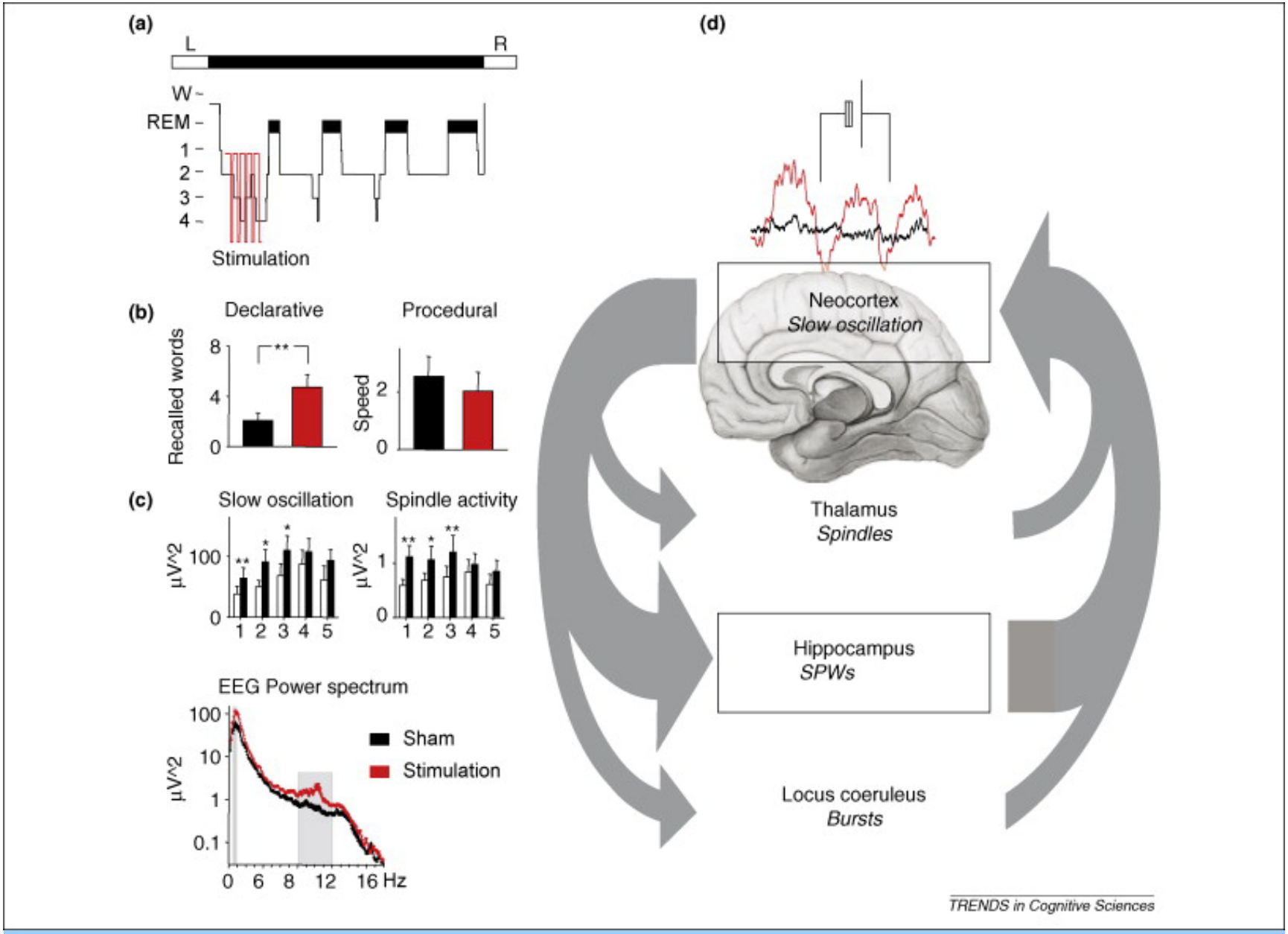
The natural shift from high levels during W to minimal levels during SWS optimizes declarative memory consolidation during a period with no need for new memory encoding

Rasch Bh et al, 2006

The contribution of sleep to hippocampus-dependent memory consolidation

Marshall L and Born J

Trends in Cognitive Sciences, in press


(a)
L
R
W
REM
1
2
3
4
Stimulation
(b)
Declarative
Procedural
Recalled words
Speed
(c)
Slow oscillation
Spindle activity
μV^2
EEG Power spectrum
Sham
Stimulation
Hz
(d)
Neocortex
Slow oscillation
Thalamus
Spindles
Hippocampus
SPWs
Locus coeruleus
Bursts
TRENDS in Cognitive Sciences

ELSEVIER

Brain Research Bulletin 63 (2004) 439–442

BRAIN
RESEARCH
BULLETIN

www.elsevier.com/locate/brainresbull

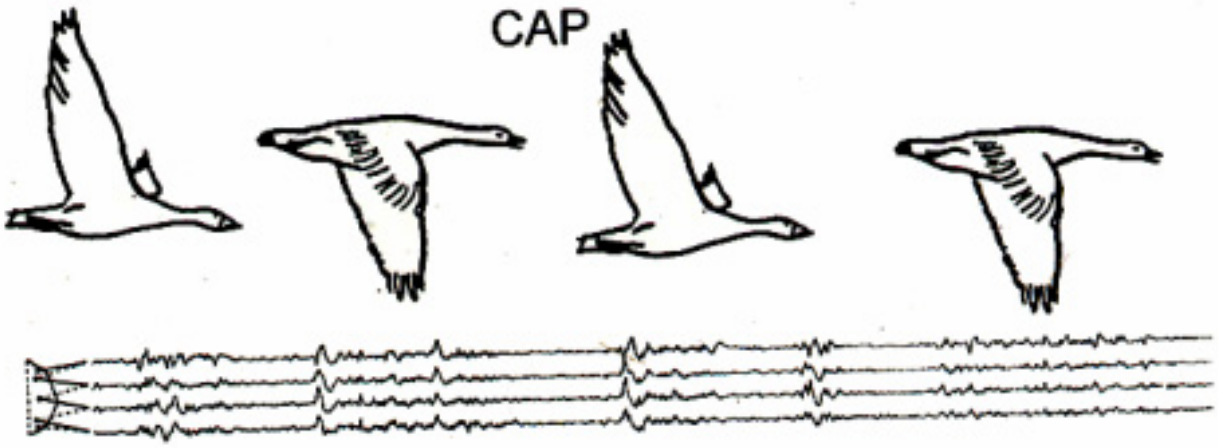
Increased periodic arousal fluctuations during non-REM sleep are associated to superior memory

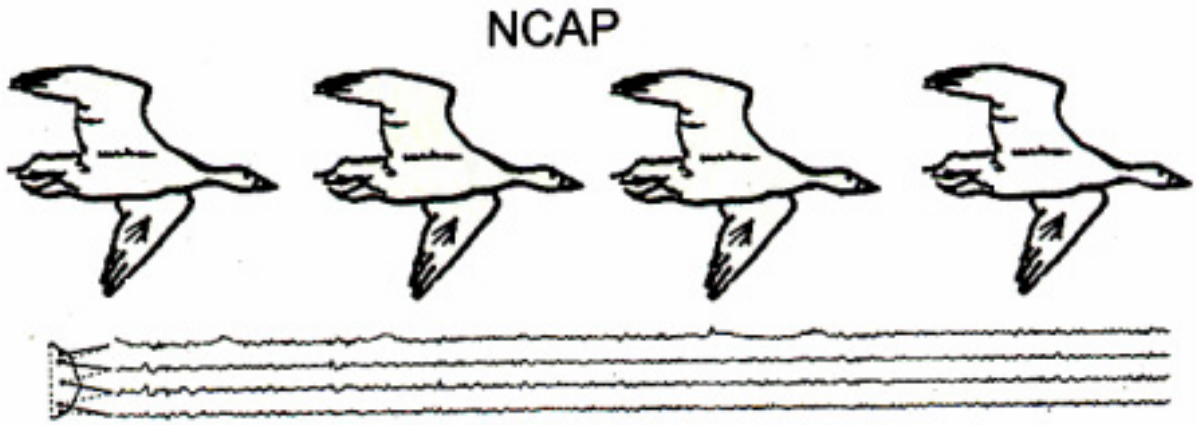
Luigi Ferini-Strambi*, Paola Ortelli, Vincenza Castronovo, Stefano Cappa

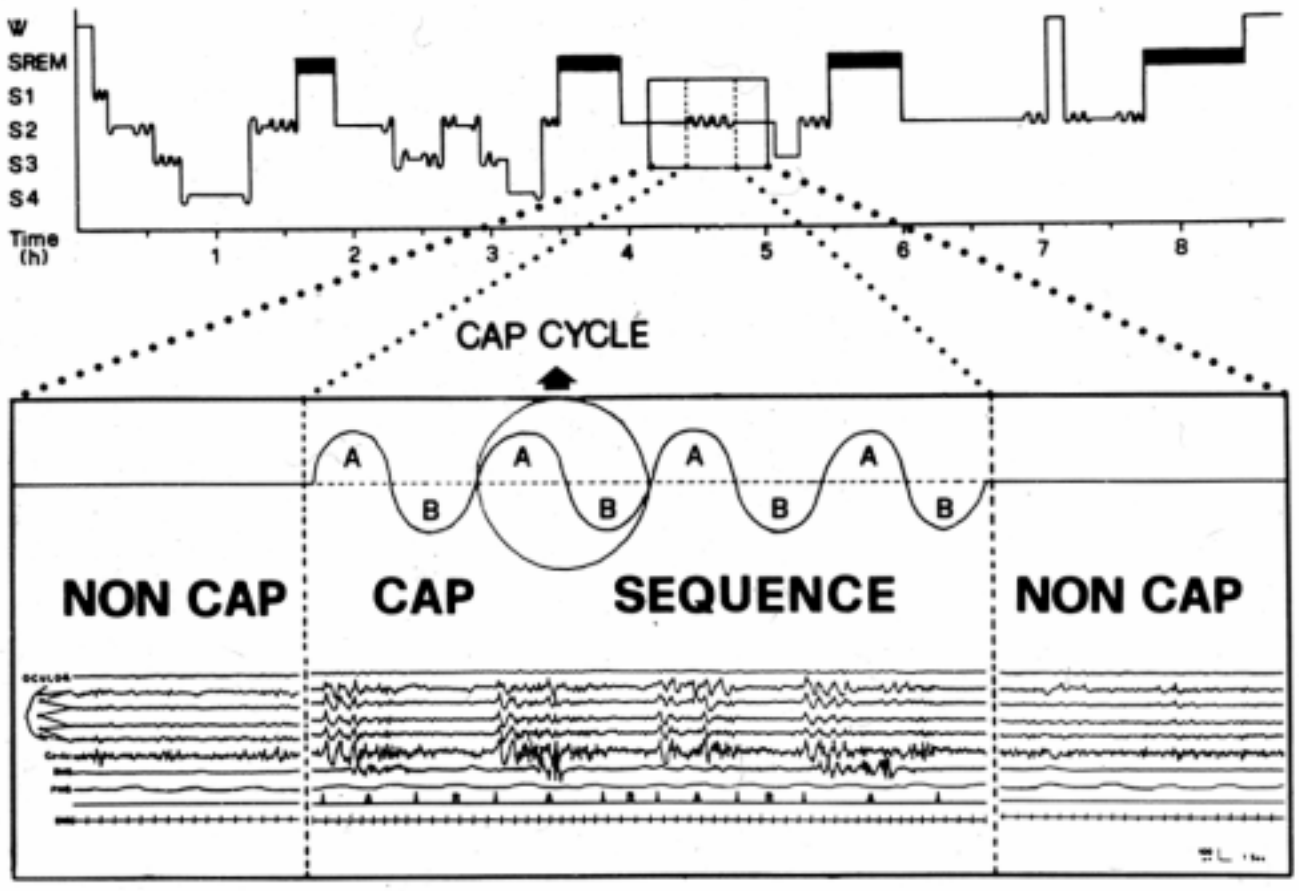
Sleep Disorders Center, Scientific Institute H San Raffaele, University Vita-Salute San Raffaele, Via Stamina d'Ancona 20, 20127 Milano, Italy

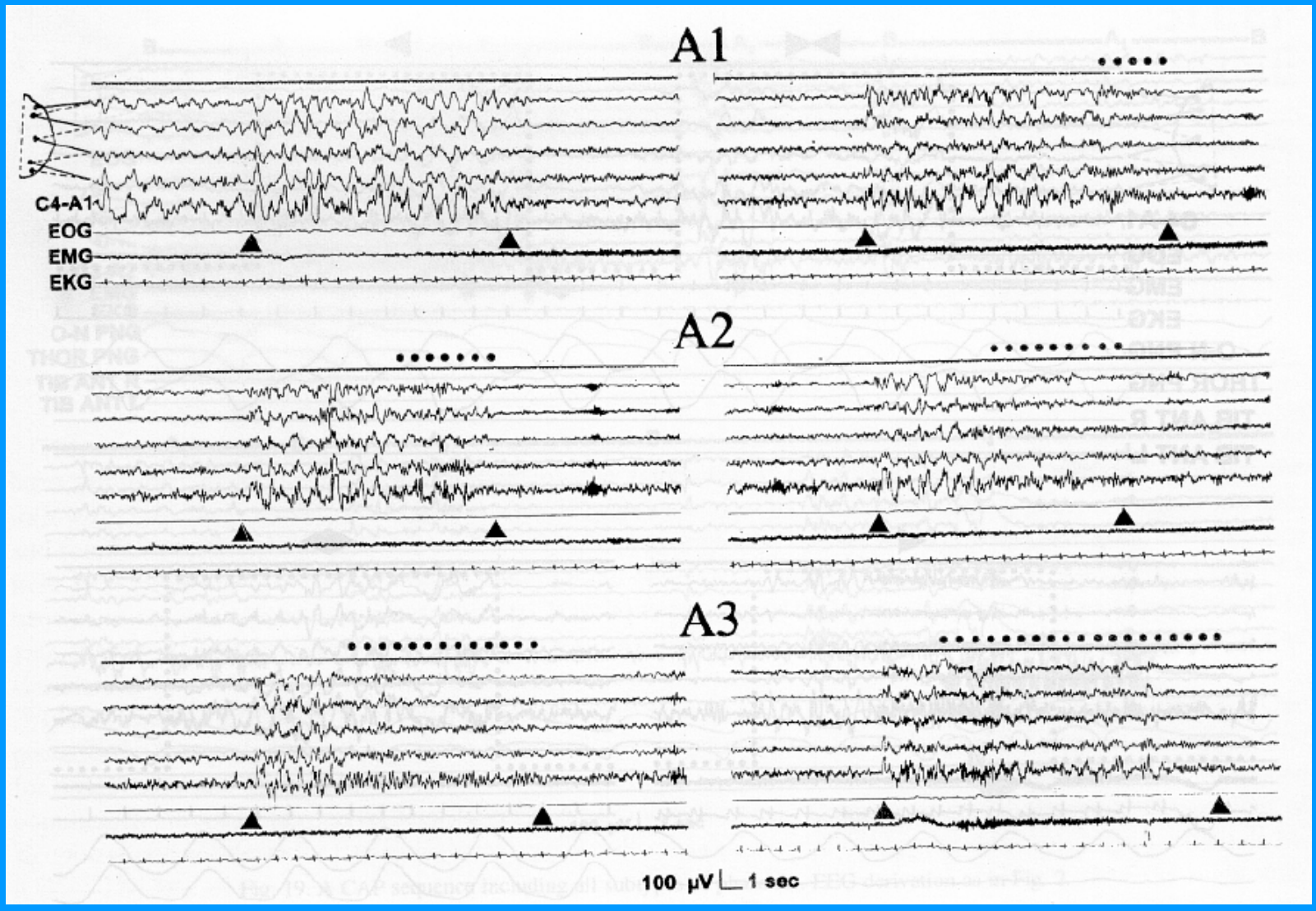
Received 18 August 2003; received in revised form 12 December 2003; accepted 20 January 2004

Available online 20 May 2004


CAP


NCAP


W
SREM
S1
S2
S3
S4
Time (h)
1
2
3
4
5
6
7
8
CAP CYCLE
A
B
A
B
A
B
A
B
NON CAP
CAP
SEQUENCE
NON CAP


A1
C4-A1
EOG
EMG
EKG
A2
A3
100 µV
1 sec

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Behavioural Brain Research 180 (2007) 48–61

BEHAVIOURAL BRAIN RESEARCH

www.elsevier.com/locate/bbr

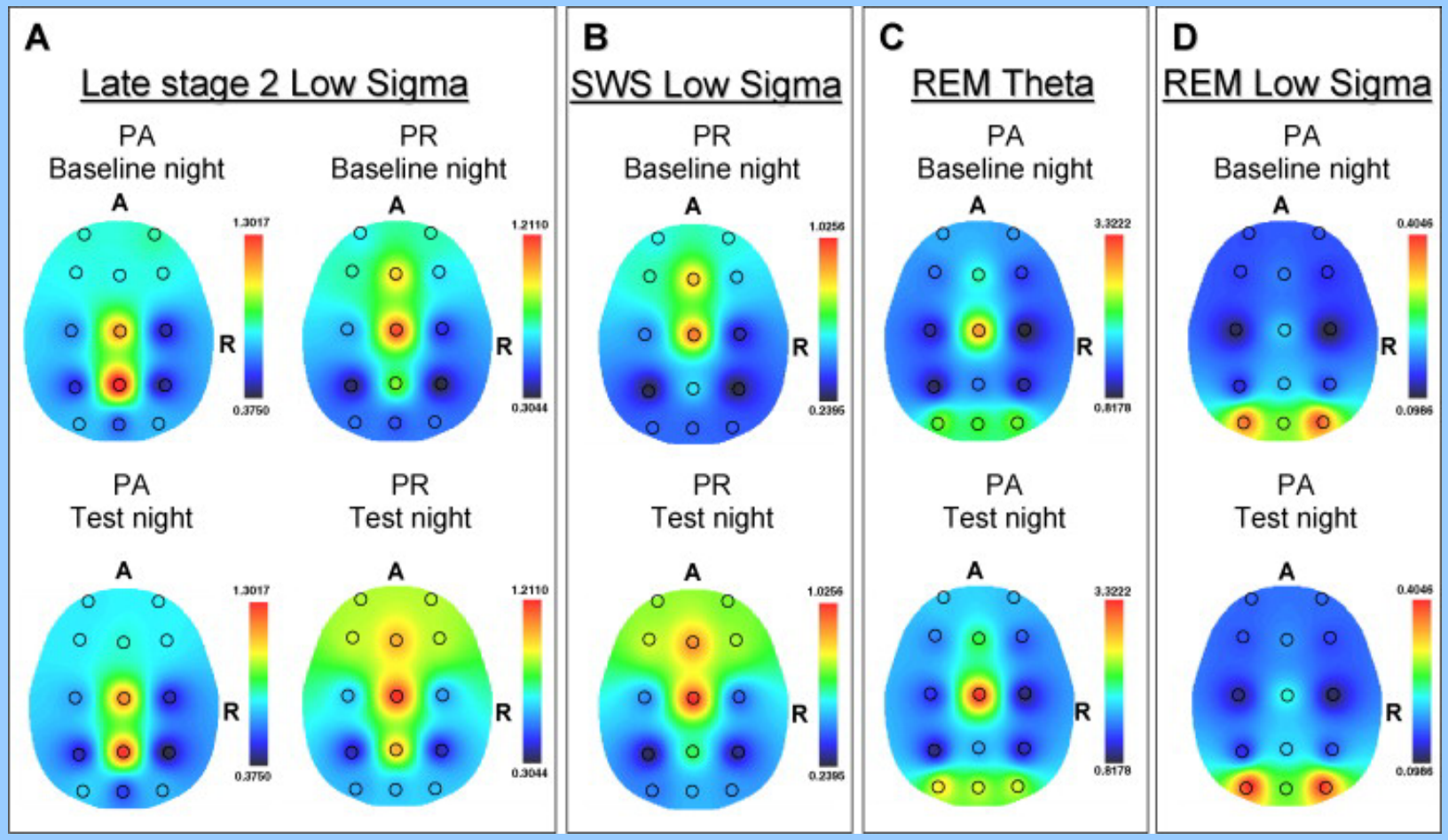
Research report

Dissociable learning-dependent changes in REM and non-REM sleep in declarative and procedural memory systems

Stuart M. Fogel [a], Carlyle T. Smith [b], Kimberly A. Cote [a,+]

Fogel MS et al, 2007

- *During wakefulness, the formation of declarative memory has been related to theta activity, which is thought to play a role in hippocampal communication with other structures*
- *Hippocampal theta predominates during REM sleep; REM sleep is an ideal time for declarative memory consolidation to occur*


A
Late stage 2 Low Sigma
PA
Baseline night
PR
Baseline night
PA
Test night
PR
Test night
A
R
1.3017
0.3750
1.2110
0.3044
B
SWS Low Sigma
PR
Baseline night
PR
Test night
1.0256
0.2395
C
REM Theta
PA
Baseline night
PA
Test night
3.3222
0.8178
D
REM Low Sigma
PA
Baseline night
PA
Test night
0.4046
0.0986

Fogel MS et al, 2007

- ***Brain plasticity during sleep does not involve a unitary process; that is, different types of learning have unique sleep-related memory consolidation mechanisms that act in dissociable brain regions at different times throughout the night.***

ELSEVIER

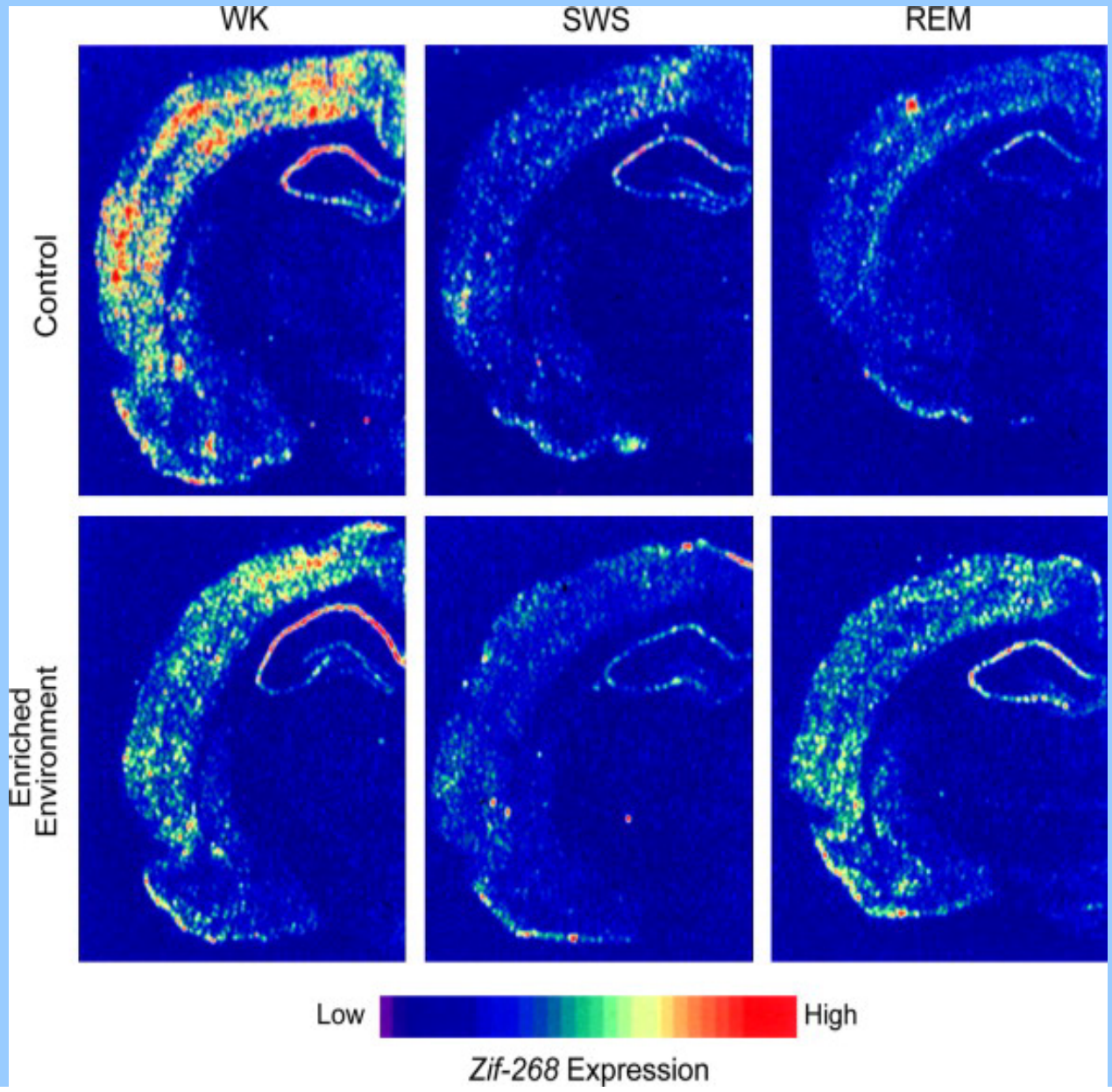
Sleep Medicine 8 (2007) 331–343

SLEEP MEDICINE

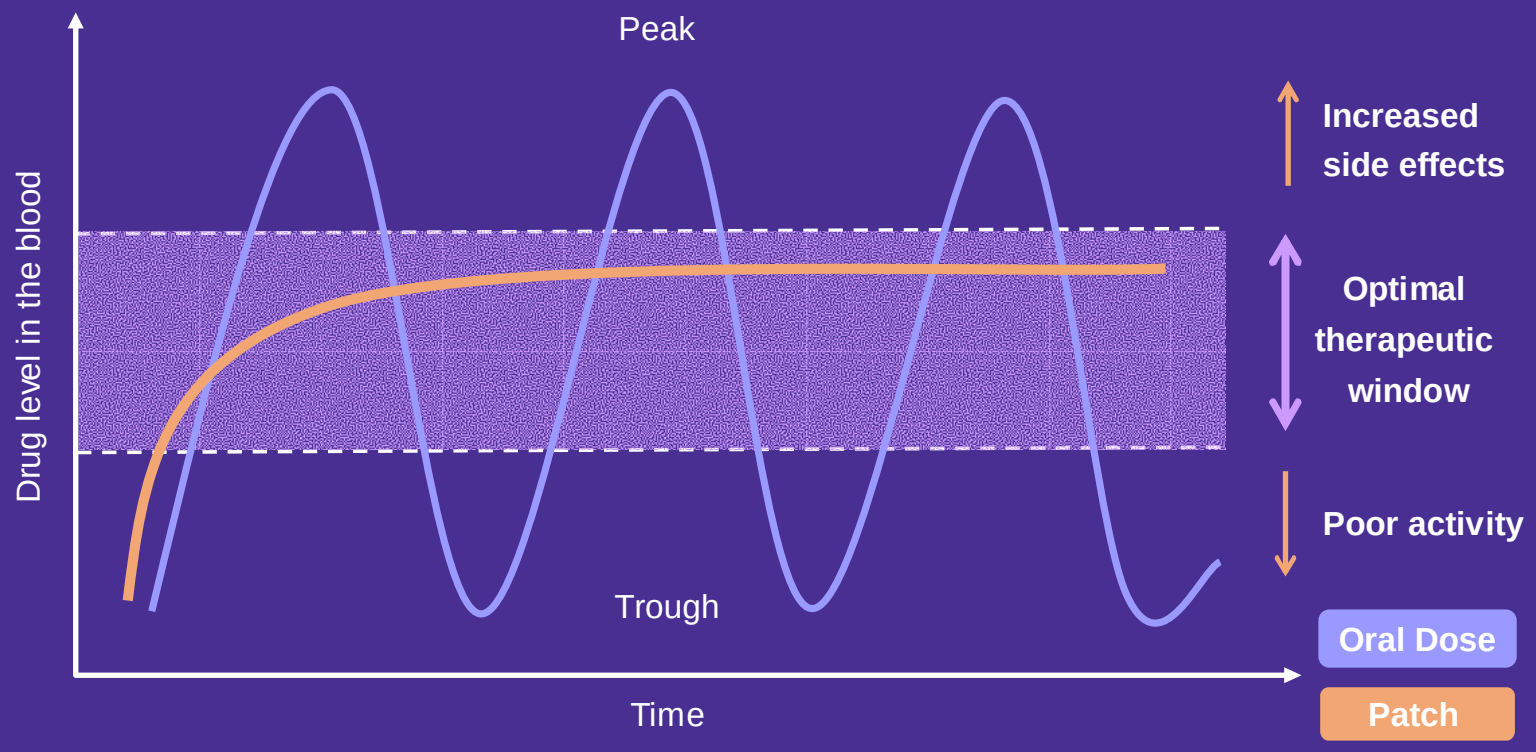
www.elsevier.com/locate/sleep

Sleep-dependent memory consolidation and reconsolidation

Robert Stickgold [a,*], Matthew P. Walker [a,b]

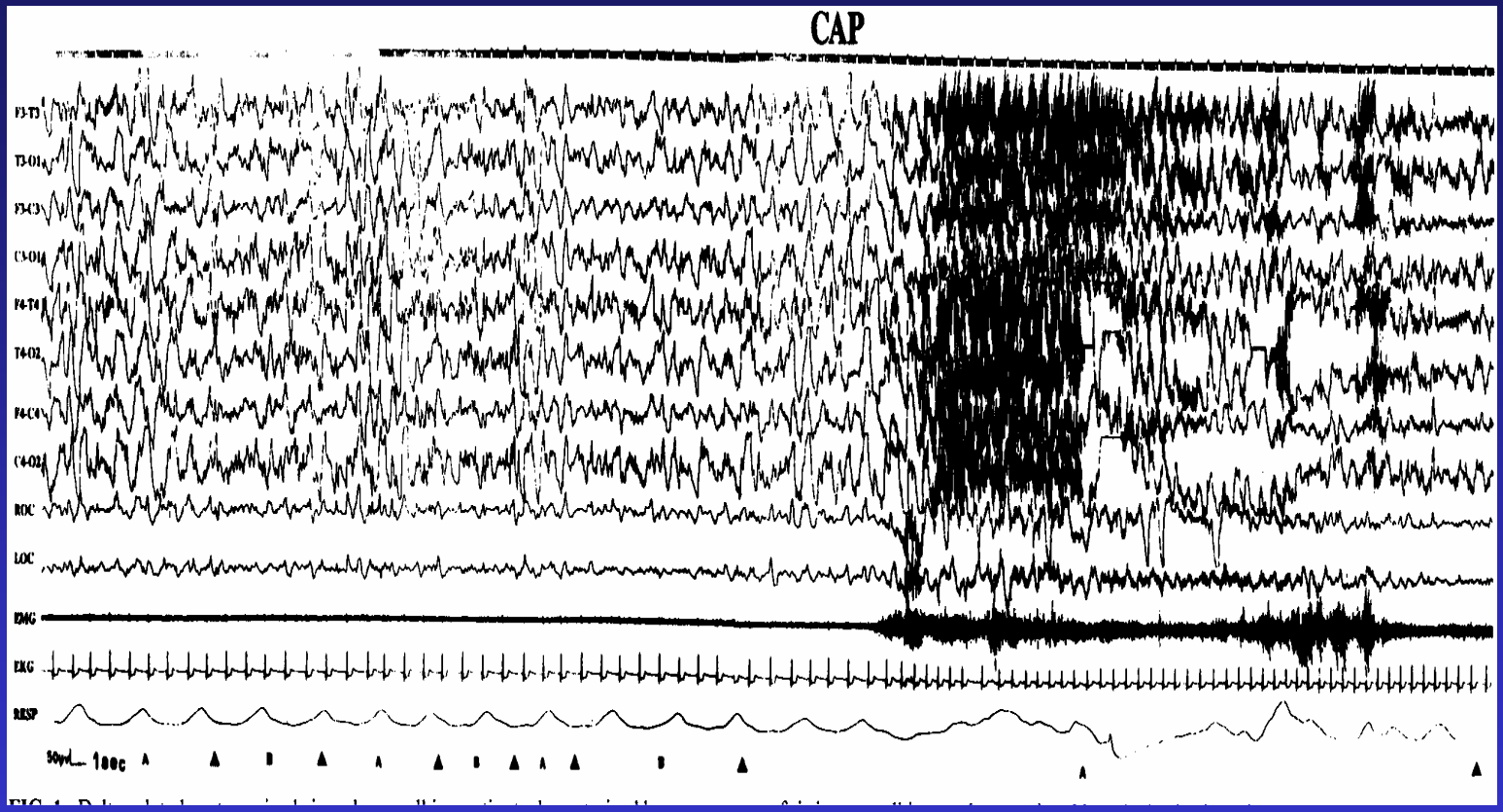

WK
SWS
REM
Control
Enriched Environment
Low
High
Zif-268 Expression

Smooth, Continuous Delivery by Transdermal Patches Keeps Drug Levels in Optimal "*Therapeutic Window*"



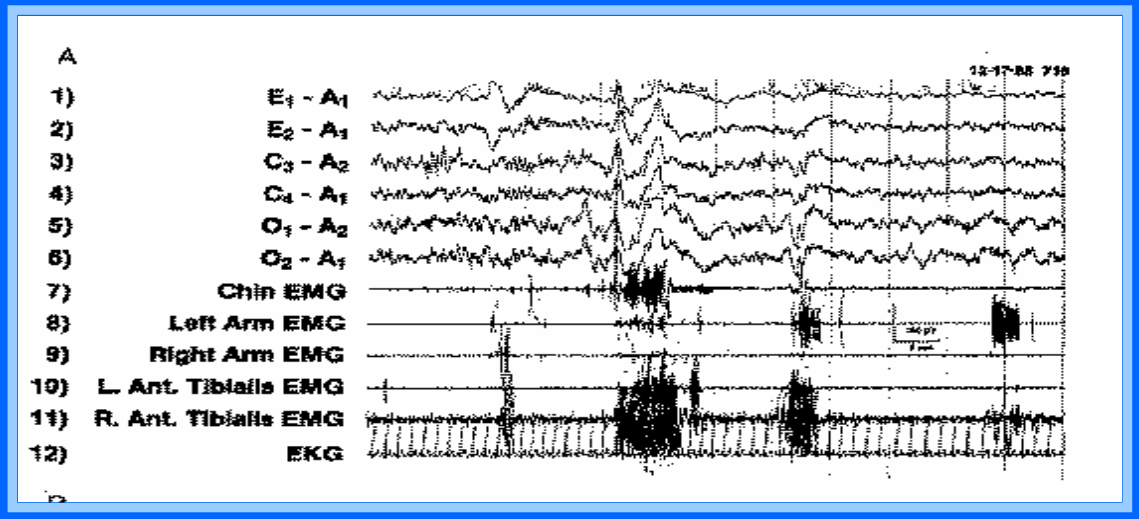
Parasonnie: Disturbi dell'Arousal

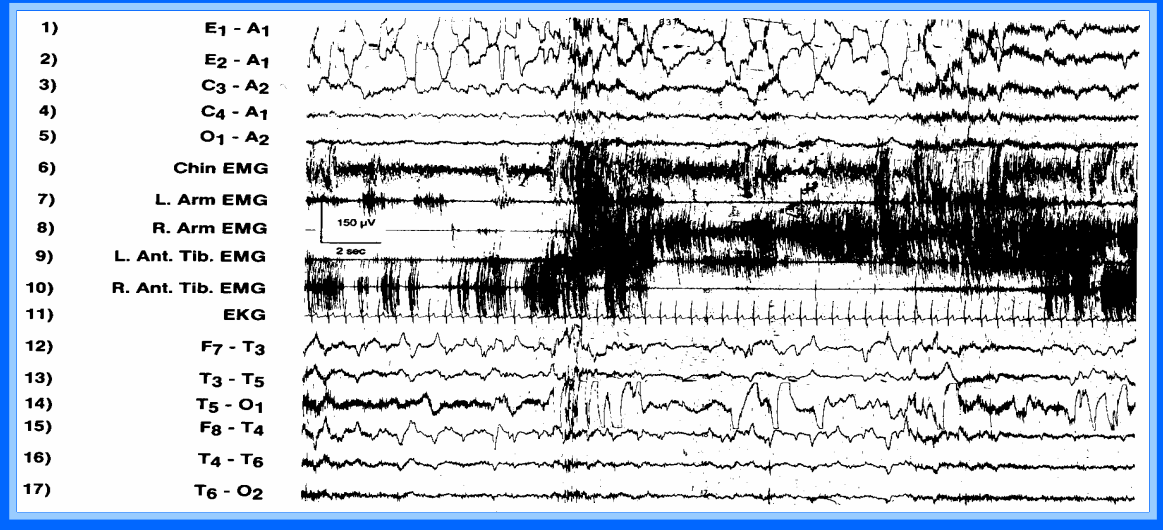
- Risvegli Confusionali
- Sonnambulismo
- Incubo dell'adulto (Pavor nel bambino)



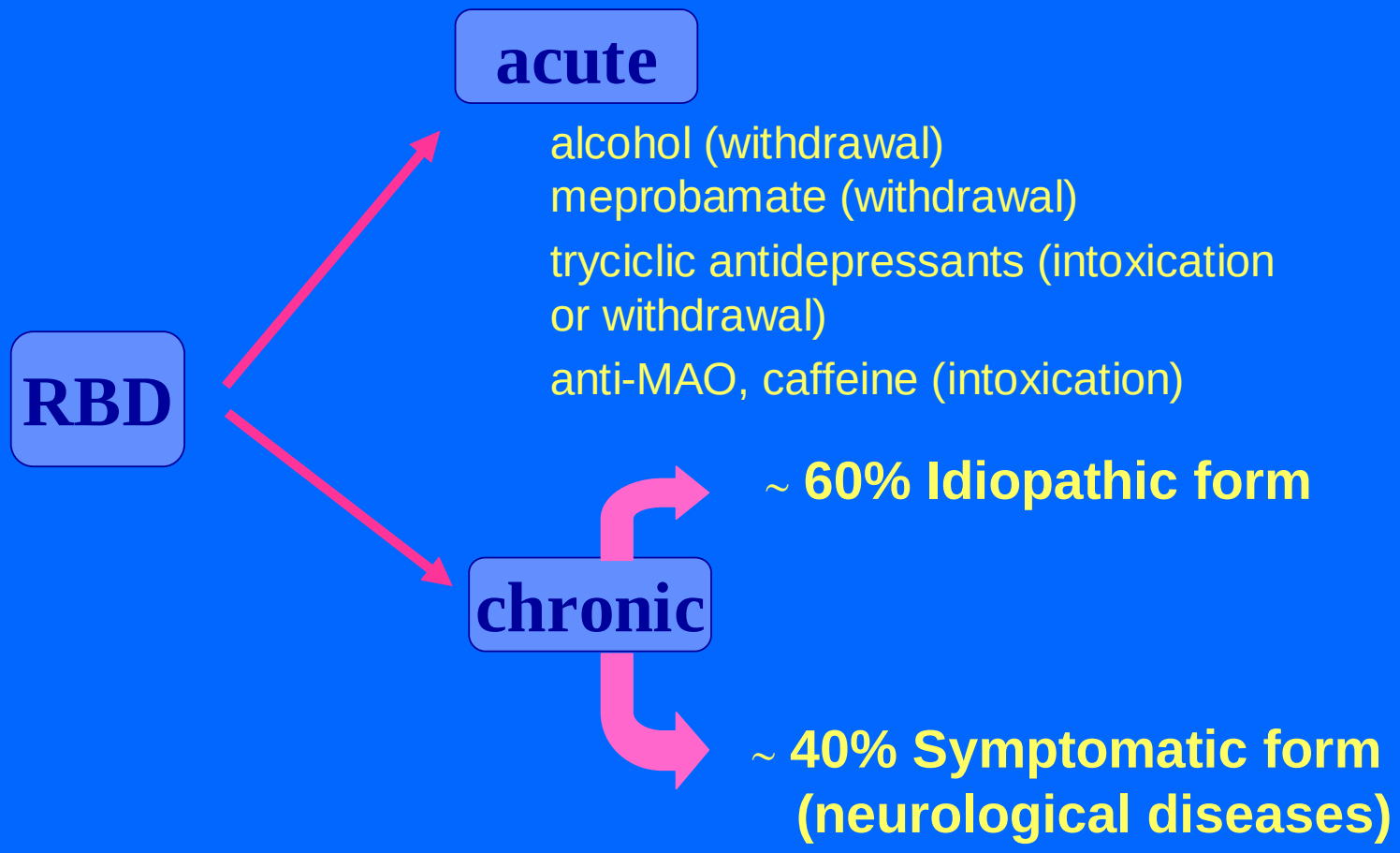
Sonnambulismo

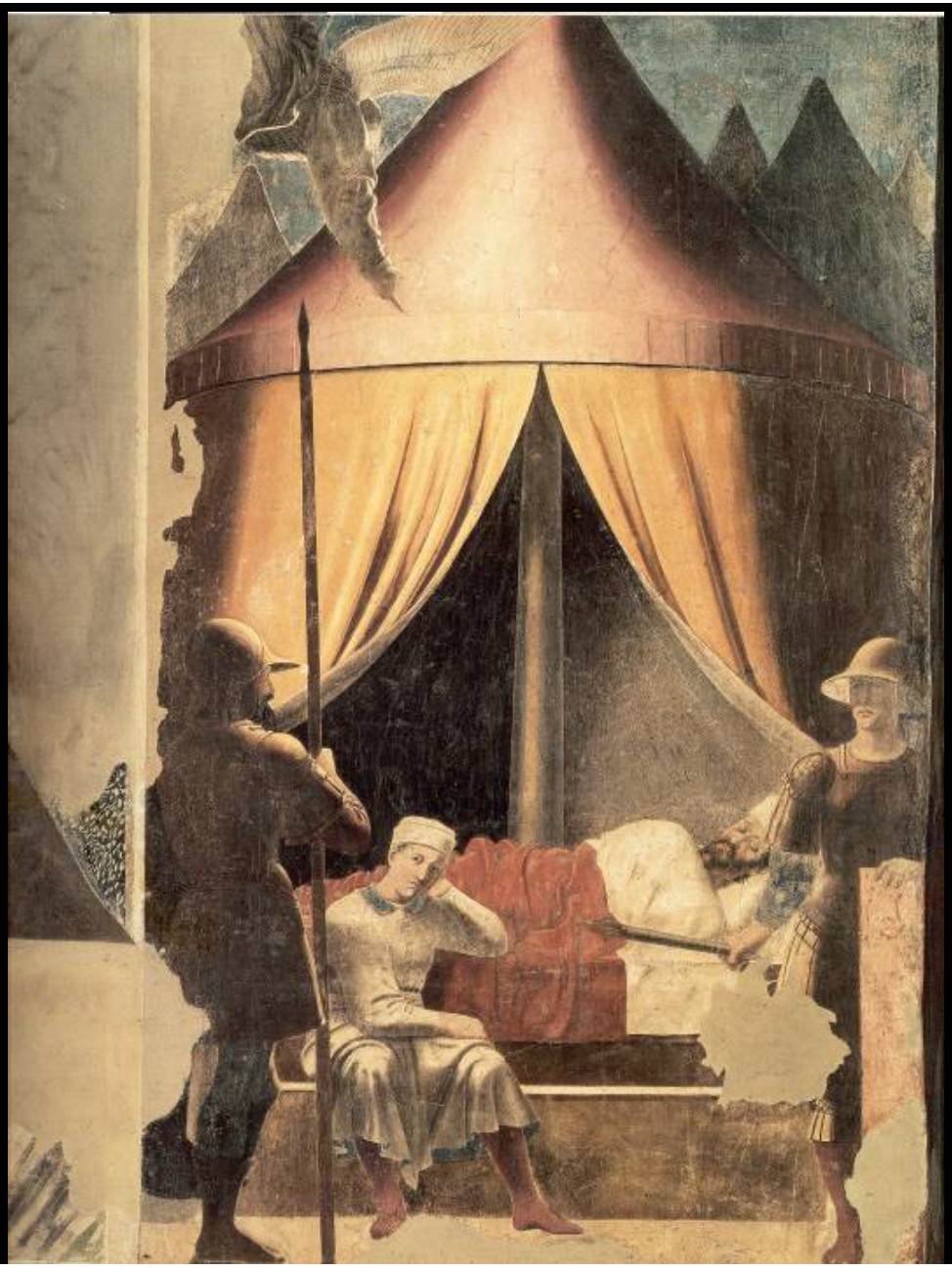
REM SLEEP BEHAVIOR DISORDER





RBD: clinical course





Il sogno di Costantino

Piero della Francesca