

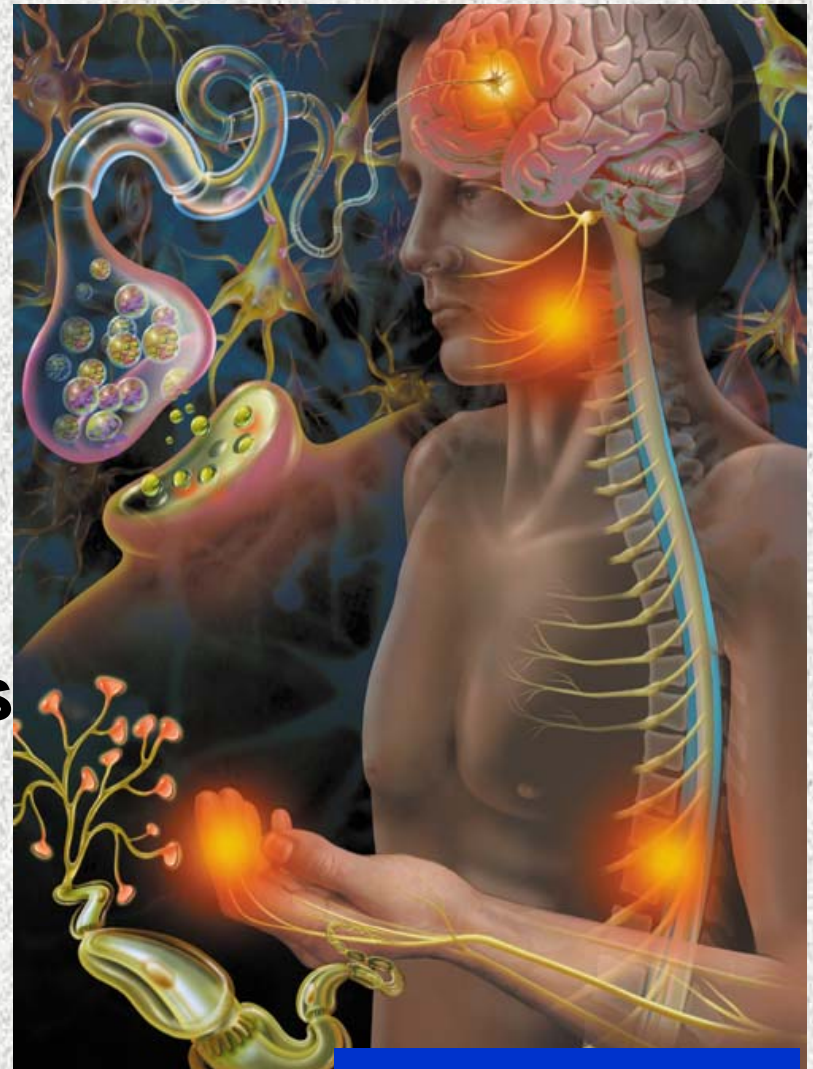


The complex history of sleep restriction on pain perception

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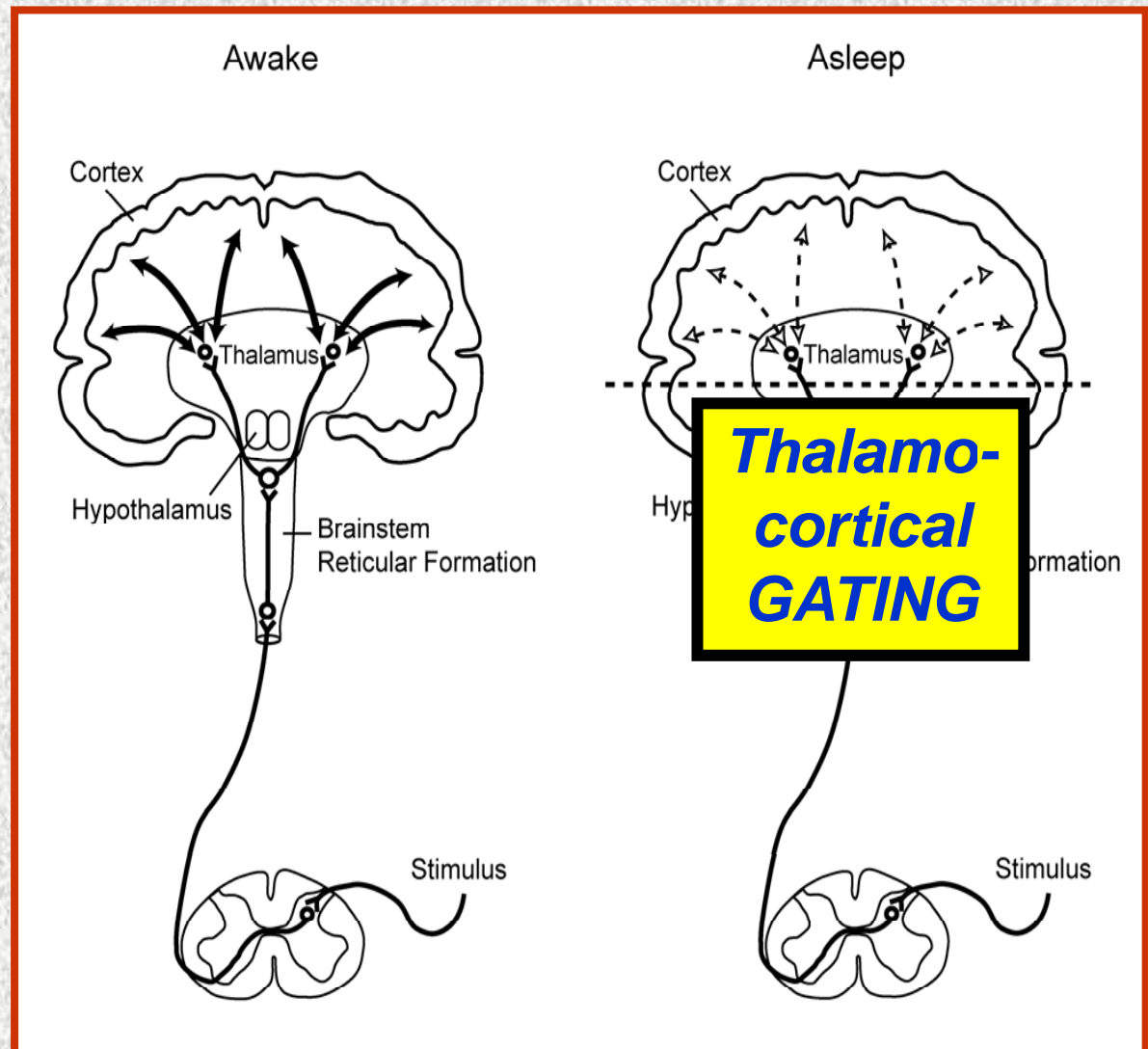
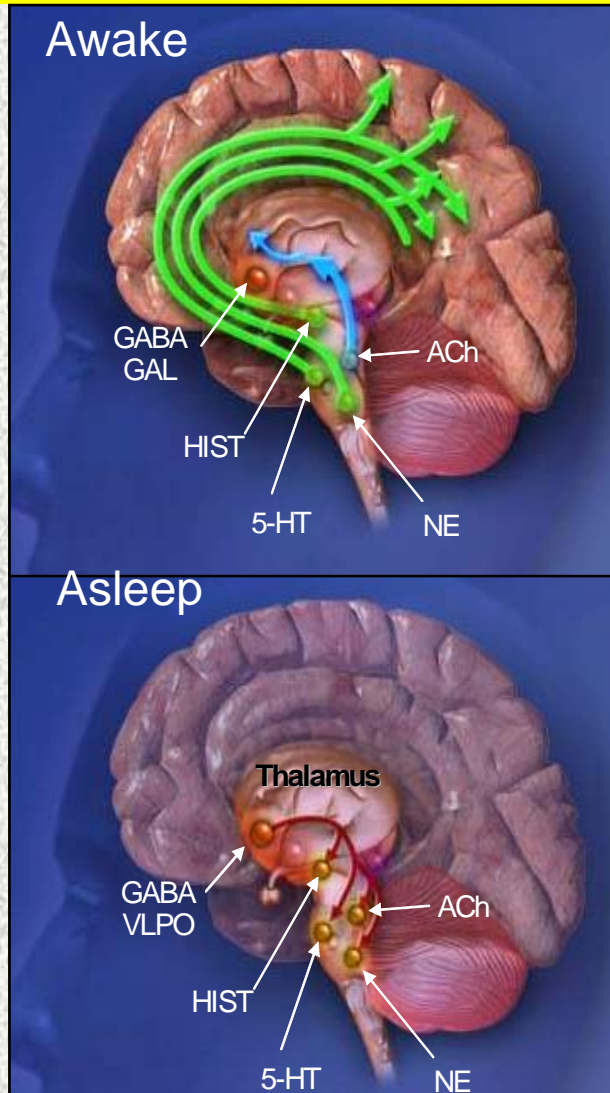
Road map of a 17 min race...

- 1. Basic understanding and pain perception during sleep**
- 2- Pain perception after sleep and Clinical findings**
- 3- Experimental challenges**



Picture from Pfizer

Cortical and brainstem networks are **PARTIALLY** isolated *from peripheral inputs* to preserve sleep continuity / homeostasis against *Fight or Flight activations* (Saper, TENS 2001; Lavigne, 2007)

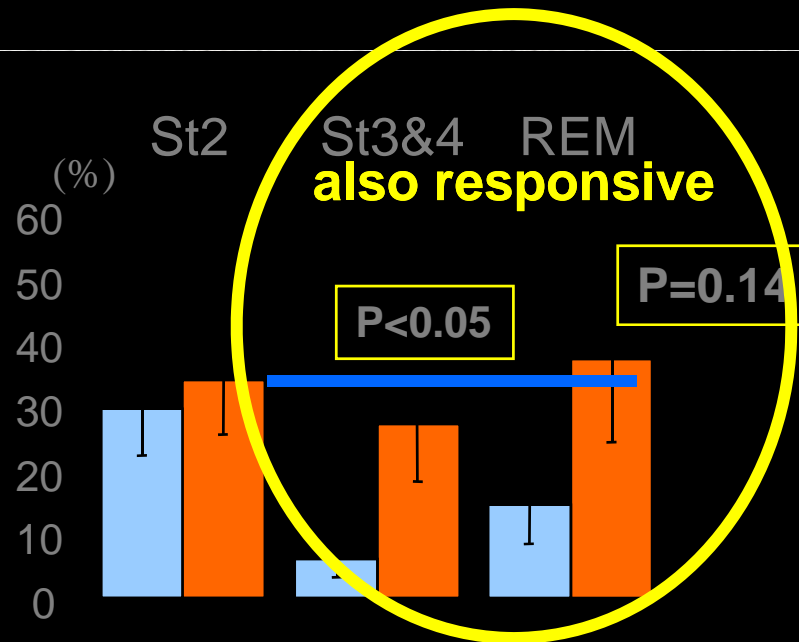


All sleep stages could be responsive to experimental pain if stimuli long enough to be processed: Difference between non-pain (vibrotactile + auditory) and pain (hypertonic saline)

Lavigne et al, Pain 2004



B. Awakening (>10 sec)



■ (Vibrotactile + auditory) - (auditory)

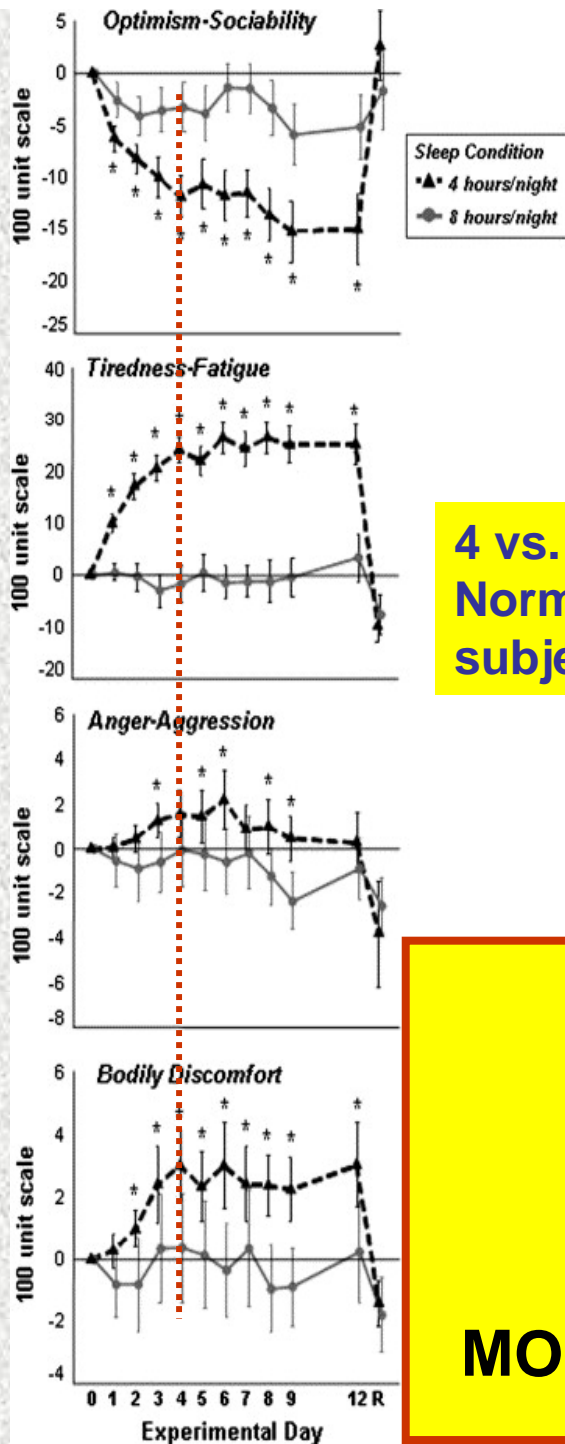
■ (Hypertonic) - (isotonic)

(mean ± SEM)

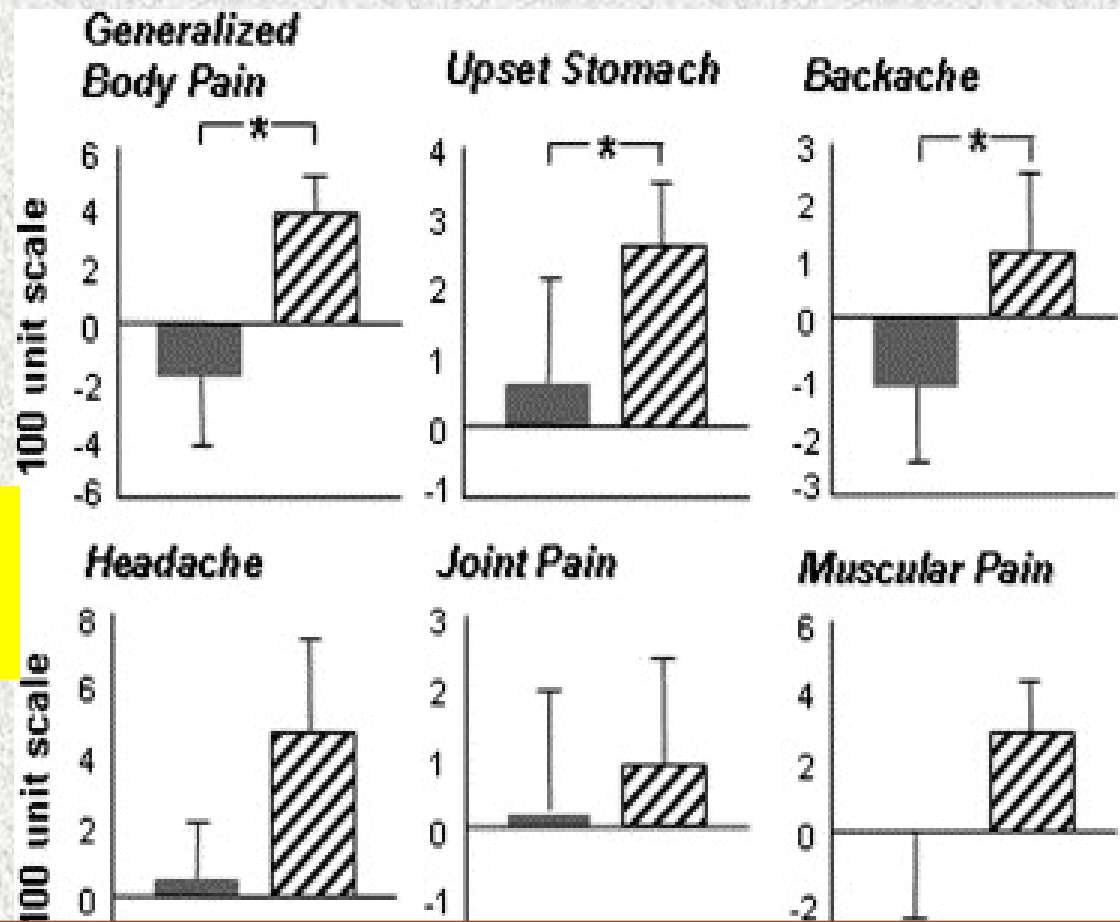
Road map

1. **Basic understanding and pain perception during sleep**
- 2- **Pain perception after sleep and Clinical findings**
- 3- **Experimental challenges**





**4 vs. 8 h
Normal
subjects**



Consistencies

**3 to 4 nights of Sleep Deprivation
(restriction in duration) =
MOOD influences & somatic Pain complaints**

Haack and Mullington, Pain 2005

Paradox on Sleep deprivation studies: most evidences based on ACUTE experiments

- Acute deprivation:

- Post surgical, travel overseas, **EXPERIMENTAL** with sound, physical presence and touch, etc
- **Can be total or selective** / few hours to specific sleep stage

- Chronic deprivation:

- **Work related** or care giver (infant, elderly), medical or sleep disorders such as PLMS, breathing, **PAIN**, etc
- ***Prevent a subject from obtaining usual amount of sleep/24 h***
- **Can be chronic or partial: SLEEP RESTRICTION**
- **15-20% pop USA sleep less than 6 h/ 24 h during week**

(Bonnet 2003, 2005; Dinges et al 2005 PPSM)

SLEEP DURATION (concept of restriction) seem to be a good predictor of next day pain

- ***If sleep is less than 6 hrs or more than 9 hrs = greater report of pain on next day*** (Edwards et al, Pain, 2008)

BUT in sleep medicine a CONTROVERSY is present regarding *too short or too long sleep duration vs. RISK of higher morbidity* (Hublin, Sleep 2007; Meisinger, Sleep 2007)

CLINICAL PAIN = MAJOR SOURCE OF SLEEP LOST / Chronic Widespread Pain clinical population

- 1- 60 min less total sleep time,
- 2- lower efficiency of sleep (% time asleep/time in bed),
- 3- 3 instead of 4-5 sleep cycles
- 4- ??? on St 3&4 duration (Okura et al, Sleep Med 2008)

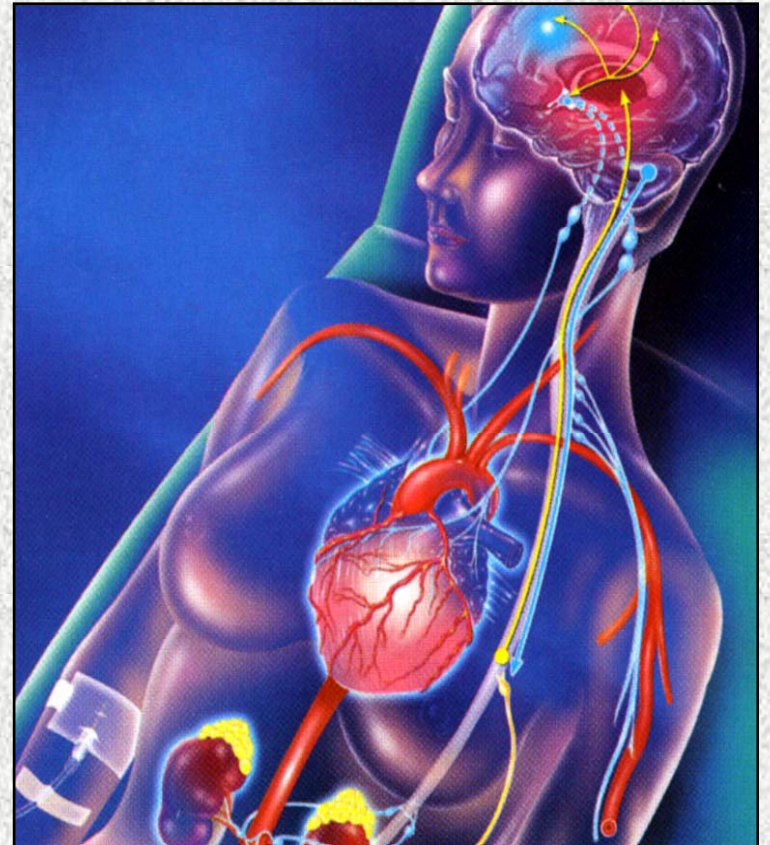
Demographics and sleep variables of normal subjects, PLMS/RLS, insomnia and chronic widespread pain (CWP) patients

Variables	Normal subjects <i>a</i>	PLMS/RLS patients <i>b</i>	Insomnia patients <i>c</i>	CWP patients <i>d</i>	<i>p</i> -value group effect	<i>p</i> -value post-hoc test
I. Demographics						
Sex distribution	5F; 5M	5F; 5M	5F; 5M	8F; 9M		
Age	54.9 ± 3.2	55.9 ± 3.1	56.1 ± 3.1	54.8 ± 2.4	0.98	
II. Sleep variables						
Sleep duration [min]	436.5 ± 10.3	411.7 ± 12.5	381.5 ± 11.2	362.0 ± 19.6	0.01	0.01^{a-d}
Sleep efficiency [%]	91.2 ± 1.5	88.1 ± 1.6	81.1 ± 2.0	80.1 ± 2.8	0.006	0.05^{a-c}, 0.01^{a-d}
Sleep cycle	4.4 ± 0.2	3.4 ± 0.3	4.5 ± 0.4	3.4 ± 0.3	0.04	
Sleep latency [min]**	11.2 ± 2.0	24.8 ± 10.8	17.5 ± 2.8	33.4 ± 14.5	0.51	
REM latency [min]*	87.5 ± 10.6	128.4 ± 27.8	76.7 ± 11.7	109.9 ± 19.6	0.53	
Awakenings/h*	5.1 ± 0.8	5.7 ± 0.9	6.9 ± 0.8	7.1 ± 0.9	0.31	
Micro-arousals/h	9.6 ± 1.6	11.7 ± 1.9	10.8 ± 0.9	9.9 ± 1.6	0.31	
Sleep stage shifts/h**	33.6 ± 4.2	31.6 ± 4.1	27.3 ± 3.5	32.1 ± 4.2	0.31	
Stage 1 [%]	11.2 ± 1.6	12.9 ± 2.2	13.9 ± 2.0	11.2 ± 1.6	0.31	
Stage 2 [%]	61.9 ± 1.9	64.4 ± 2.1	61.5 ± 2.0	65.1 ± 2.1	0.31	
Stages 3 and 4 [%]**	7.0 ± 2.6	5.8 ± 2.6	3.3 ± 1.9	5.1 ± 2.6	0.31	
REM [%]	19.8 ± 1.3	16.9 ± 1.3	21.3 ± 1.8	17.1 ± 1.3	0.31	
PLMS index**	2.0 ± 0.9 (9)	33.4 ± 3.4	1.7 ± 0.8	8.1 ± 1.3	0.31	

Female CWP/ctl = 25% less REM time
Female CWP/male CWP = 2.6 X less Stages 3&4

Road map

1. **Basic understanding and pain perception during sleep**
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3.1= Pain rating (mechanical, thermal modalities) during wake in relation to sleep deprived normal subjects = hyperalgesia (more sensitive to pain stimuli) in most studies

(see Lautenbacher reviews in 2006, 2007)

Threshold studies = first time heat or pressure is perceived as painful (50% of time)

Pain tolerance studies = max can be supported before OUCH!

First experimental challenge (sound induced deprivation- morning awake pain tests /// gender & fatigue issues):

- **Original findings from Moldofsky and Scarisbrick 1976 =**

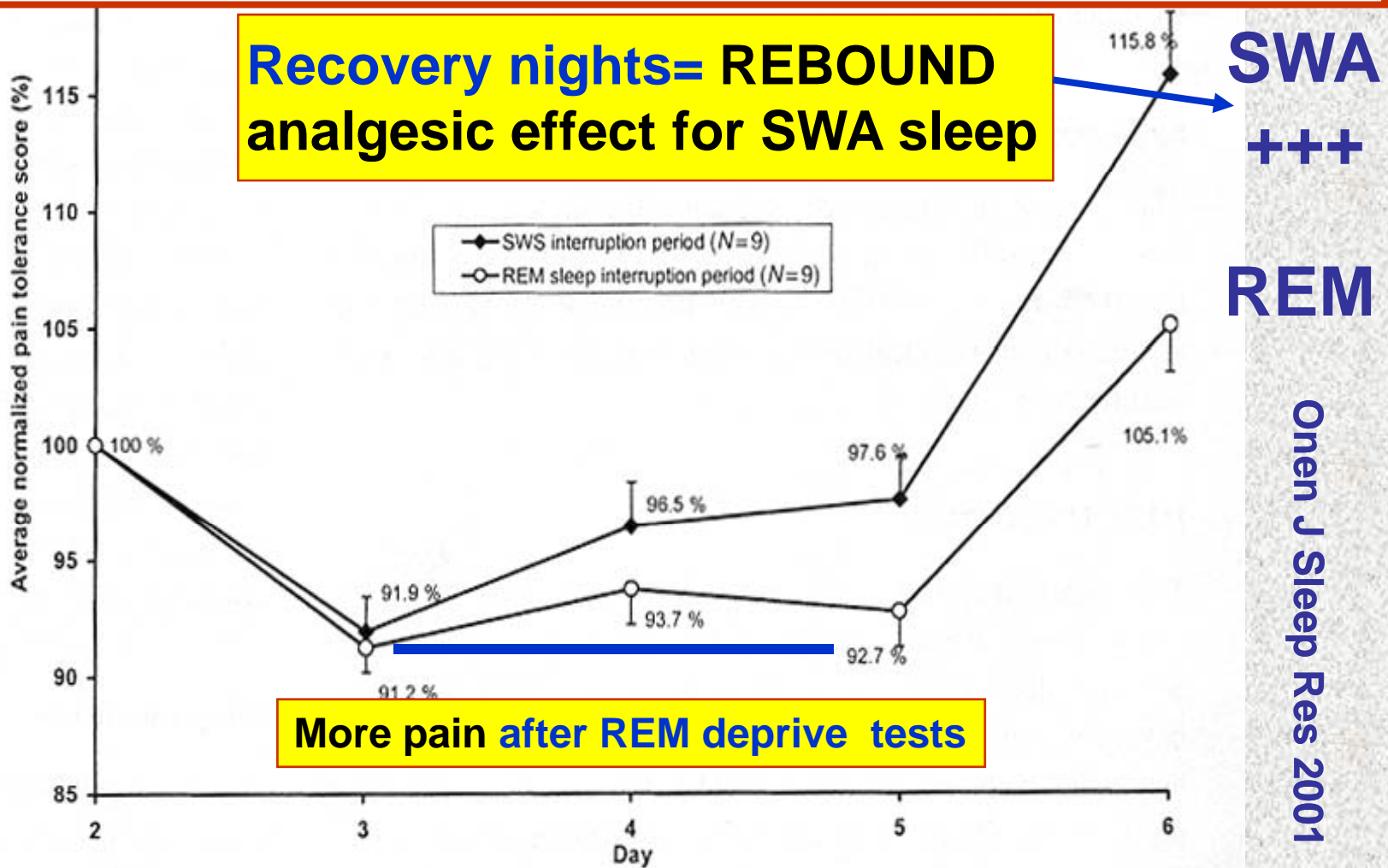
*The deprivation of sleep St 4 (n=6) in normal MALE (9/10) subjects = more musculoskeletal mechanical **TENDERNESS** than in the REM sleep (n=4) deprived subjects*

+ = DATA related to deprivation of Slow Wave Sleep were reproduced by Lentz et al (J Rheumatol 1999) for pain perception (mechanical threshold = 24% lower) in morning // only FEMALE normal subjects (NB: no effect on ALPHA-DELTA sleep)

- = NOT reproduced by Older (J Rheumatol 1998) **due to influences of FATIGUE in normal** (M/F=13/6) subjects **compared to fibromyalgia patients** (M/F= 6/1)

**Deprivation of sleep stages SWA or REM = lower mechanical pain tolerance (8% and more stable for REM deprivation)
 BUT analgesic rebound for SWA / recovery night**

Pain tolerance = max can be supported before OUCH!

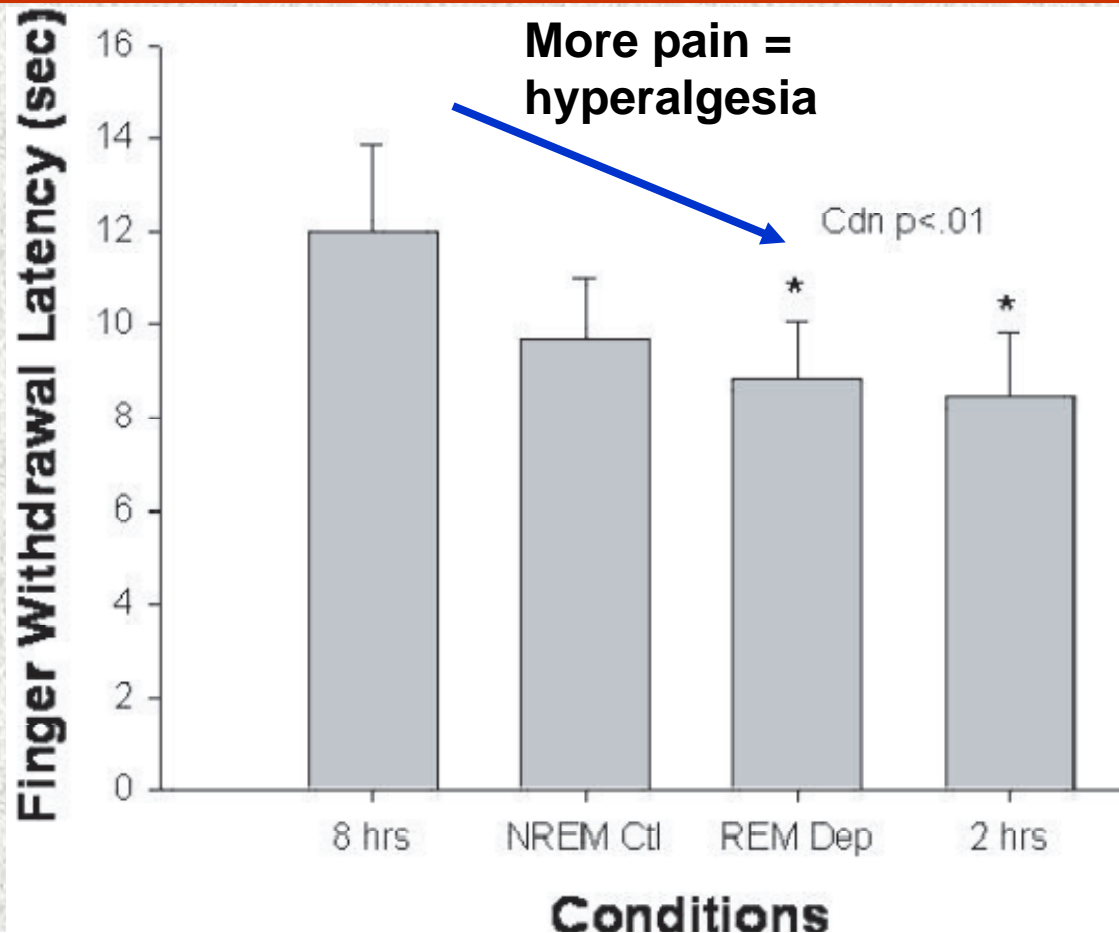


No specificity for REM deprivation! *RESTRICTION*

Both REM sleep stage deprivation and 2 hours of sleep restriction = hyperalgesia

lower mechanical pain threshold
(Normal male and female)

Threshold study =
first time heat or pressure
is perceive as painful

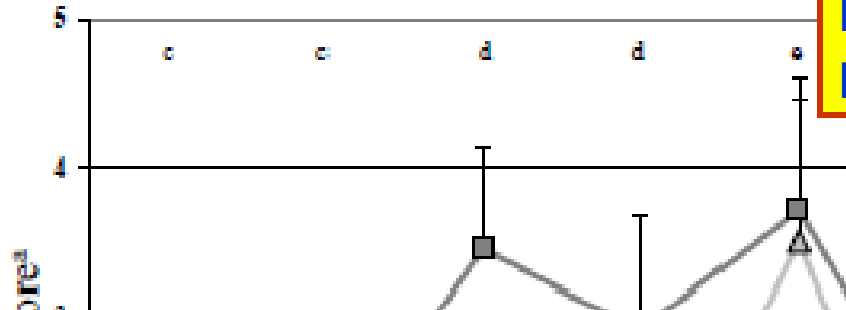


Roehrs et al, SLEEP 2006

Disturbance of SLEEP CONTINUITY may be more important:

Forced awakening FA (blocks of 60 min sleep / wake) vs. Restricted sleep (delayed sleep onset) in NORMAL SUBJECTS

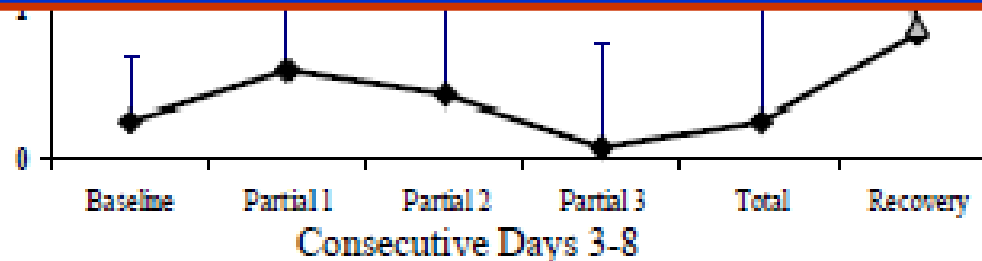
A. Painful Symptoms (PILL)



Forced awakening = higher somatic pain reports

Smith et al

Chronic widespread pain patients (FM) have 50% more cyclic arousal shifts during their sleep (Rizzi et al 2004)

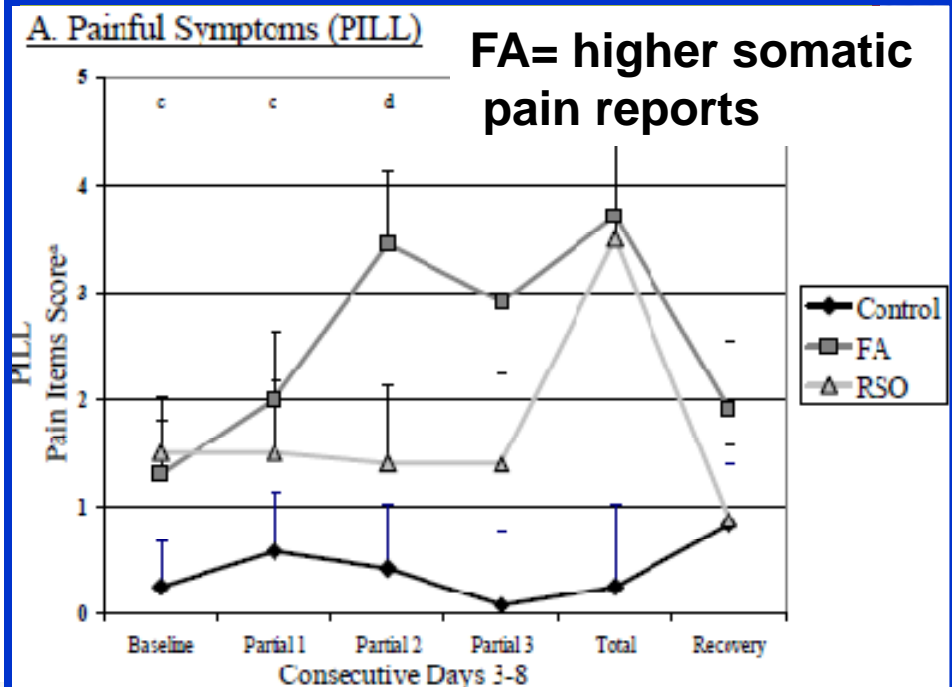
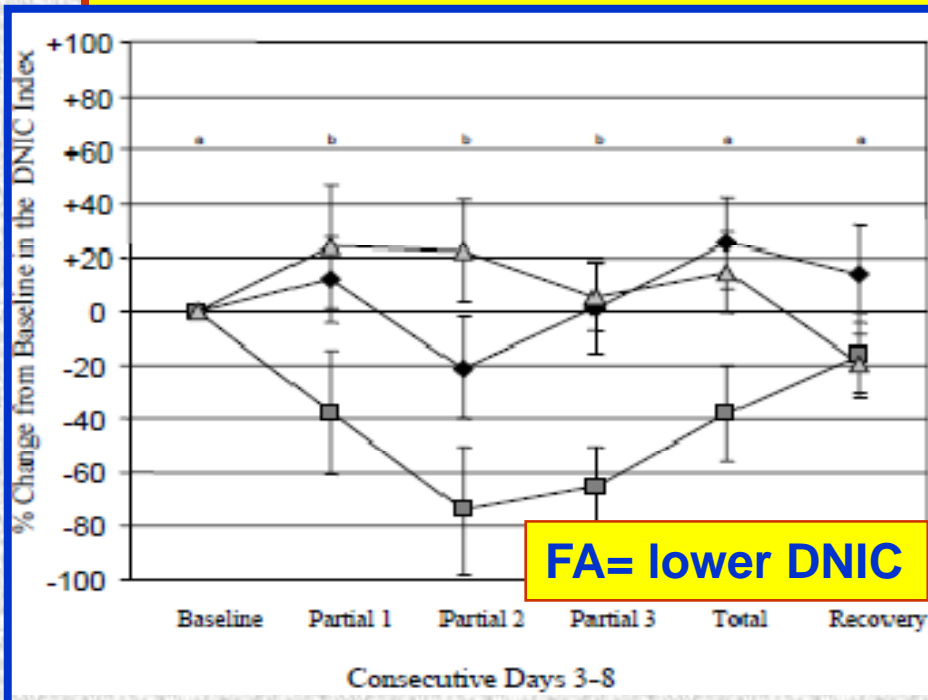


DISTURBANCE OF SLEEP CONTINUITY *Forced awakening* *FA* (blocks of 60 min sleep / wake) vs. *Restricted sleep* (delayed sleep onset) in NORMAL SUBJECTS =

1- **dysfunctional - DNIC (diffuse inhibitory analgesic control) = natural analgesia mechanism;**

2- AND, higher somatic pain reports

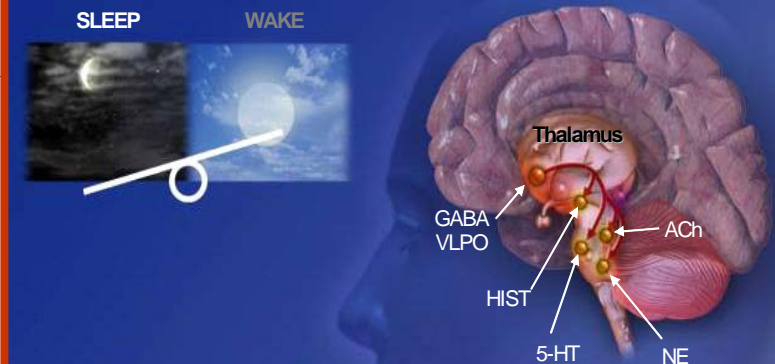
Pain testing DNIC (cold) and PPT_h (Smith, Sleep 2007)



Rat studies and hyperalgesia following REM deprivation: new pathways for drug development in pain and sleep interaction?

- Reduced by 5-HT (1a) and (2) receptor antagonist, by 5-HT (1a) agonist but not by serotonin 5-HT (3) related compounds administered intrathecally – mechanical test (Wei, Pharmacol Res 2008)
- Glutamate 5 receptor antagonist and Nitric Oxide synthase (NOS) inhibitor = same reducing effect on hyperalgesia to mechanical stimulation following REM deprivation or peripheral nerve injury (Wei, Brain Res 2007)
- See reviews from Lautenbacher 2006 Sleep Med Rev, 2007 IASP Press

Sleep System



Saper et al

**Central sensitivity syndrome
(see Yunus 2008 for FM):
are they pain or vigilance
state specific?**

**3.2= Pain rating during wake
in relation to sleep
in *normal subjects***

***Mood influences (short REM
latency)***

and

***Patient expectation (placebo
conditioning study – Laverdure D)***

Change in AWAKE experimental pain THRESHOLD in relation to REM sleep duration

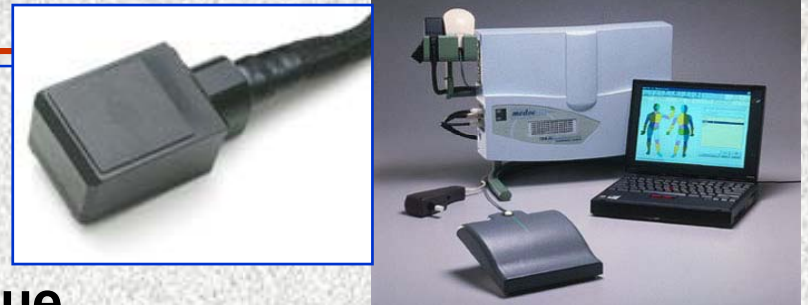
(Normal subjects, female only) Smith et al, Sleep 2005

A- Thermal Pain Perception

Heat Pain Threshold (oC)

Afternoon 2	Afternoon 3	p value
42.49 (3.78)	42.51 (3.55)	.549

NO DIFFERENCE



Threshold study = first time heat or pressure is perceive as painful

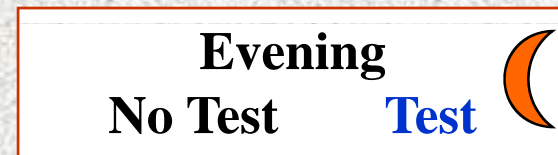
B- Correlation between pain perception reported on 100 mm VAS and sleep stage duration

	REM %	REM Latency	SWS % (NREM 3+4)
Heat Pain Threshold (HPTH)	-.01		
Mean Suprathreshold Ratings	.60 (p= 0.014)	-.66 (p=0.005)	-.31

More sleep in REM = More pain BUT MOOD INTERACTION since short REM latency...

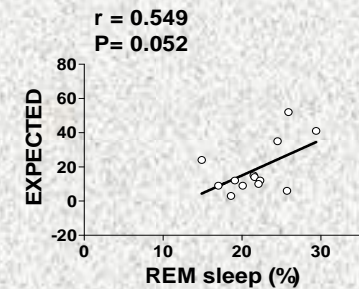
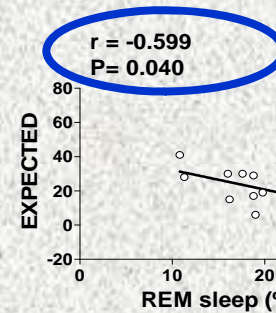
PLACEBO Analgesia conditioning and EXPECTATION

- Subject told test new analgesic cream in comparison to placebo inert cream (Price paradigm, U of Florida, USA)
- Temperature set 2 degree lower to mimic analgesic effect



Intensity

Intensity



OPPOSITE effect on EXPECTED ANALGESIA:

Shorter REM = more expectation of analgesia in placebo responder subjects
Conditioning influence!

Laverdure-Dupont, Rainville, Montplaisir, Lavigne
APSS abstract 2007

A challenging Paradox for PAIN assessments (S Khoury, PhD student)

- Do QST done in best time to collect a valid response? Alertness and memory disturbances
- Possible **PHASES DELAY** may influence estimations of pain assessments?



Phase shift in 40% of patients= to sleep about 25 min later and wake 75 min later

--- 10 to 20 min worst if not at work ---