Sleep Fragmentation as a cause of Excessive Daytime Sleepiness

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Case 1: 0-10 years

Andrew, 9 y/o

Sleeps in class, disinclined to play – "*Tired*"

Naps when he gets home from school and often twice a day on weekends.

Met with Guidance counselor at school – Nil to report

Appointment with Child Psychiatrist – No problems, no family problems

3 year History: ??Started after minor dog bite

Sleep Consultation: Nil of note.

Bedtime ~9:30pm, Awakes ~7am

Case 1: 'Andrew' Continued

Sleep Study: Tuesday

Study Start: 9:30pm

Sleep Latency: 14 min

REM Latency: 74 min

Sleep Stages: Normal for age

Arousal Index: 18/hour

AHI: <1/hour

PLMS: 2/hour

MSLT:

Time	9am	11am	1pm	3pm	
SOL	7 min	2 min	4 min	11 min	**mean** 6 min

No REM sleep

What would you do?

Case 1: 'Andrew' Continued

Andrew has an increasing dose of trypthphan over a 12-week period.

The final dose is 3 grams one hour before bedtime

Parents note a clear improvement.

Teacher is so moved with results: writes to sleep clinic.

Repeat Sleep Study: Friday

Study Start: 9:30pm

SOL: 8 min

REM Latency: 82 min

Sleep Stages: Normal for age

Arousal Index: 2/hour

AHI: <1/hour

PLMS: 2/hour

MSLT:

Time	9am	11am	1pm	3pm	
SOL	-	-	18 min	-	**mean** 19.5 min

No REM sleep

No Sleep Fragmentation = Sleepiness gone!

Case 2: 10-20 years

Cathy, 17 y/o. Seen in another sleep clinic for 'insomnia'.

Following consultation, they note:

She goes to bed 1-2am weeknights and has a hard time getting up for school.
She goes to sleep on weekends at 2-4am and sleep in late.
Tired during daytime

Sleep Study (at that clinic):

Study Start: 11pm
SOL: 194 min
REM Latency: 62 min

Sleep Stages: Disrupted
AHI: 0/hr
PLMS: 6/hour
Arousal Index: 26/hour

MSLT: Not done

Patient was prescribed zopicline: did not help! Sleep diary not kept. Told of website for sleep hygiene. No further help offered in that clinic.

What would you do?

Case 2: 'Cathy' Continued

We did a sleep consultation.

- Phase Delay seemed most likely (not considered in other clinic's report)

Protocol of 2 nights:

1st Night

PSG: "Early" sleep
bedtime before midnight

Night 1 Results:

Low sleep efficiency; prolonged SOL

High arousal rate (21/hr)

Day

MSLT

MSLT Results:

SOL: 13 minutes av.

(SOL for 4 sessions: 5min, 8min, 17min, no sleep)

No REM

2nd Night

DLMO: 7pm-3am

PSG: 3:30-10:30am

DLMO Results: Clearly delayed melatonin onset

Night 2 Results:

Normal sleep efficiency

High arousal rate (18/hr)

REM onset early

What would you do?

Case 2: 'Cathy' Continued

Single-Blind melatonin/placebo administration

Clear positive response to melatonin

Remained on melatonin for 1 year

Repeat Sleep Study: Wednesday (on melatonin)

Study Start: 11pm

SOL: 19 min

REM Latency: 96 min

Sleep Stages: Normal for age

AHI: 0/hr

PLMS: 4/hour

Arousal Index: 18/hour

MSLT:

Time	9am	11am	1pm	3pm	
SOL	-	-	19 min	-	**mean** 19.75 min

No REM sleep

No Complaints!

Case 3: 20-30 years

Ahmed, 24y/o Iranian student at Univ. of Toronto

Referred for '*poor sleep*'

Complains of initial/maintenance/terminal insomnia & unrefreshing sleep

Questionnaires: 14/20 physical complaints; ESS: 15; FSS: 6.5;
ZOGIM-A: 12; CES-D: 17, Rosenberg: normal

Interview:

Asked about triggers, stress, mood without any useful info emerging.

Ahmed had been on Temazepam 30mg then 60mg for 1 month. No benefit.

Sleep Study: Saturday

Study Start: 10:30pm

SOL: 38 min

REM Latency: 48 min

Arousal Index: 26/hour

MSLT: not done

AHI: 0/hr

PLMS: 0/hr

Sleep Stages: Very little SWS in 1st two hours of sleep.
Reduced total SWS

What would you do?

Case 3: 'Ahmed' Continued

Depression Balance Sheet

Clinical: -ve

Sleep Markers: +ve

Questionnaires: +/-

Trial of Mirtazepine suggested: Patient ambivalent

"Buys into" low dose (15 mg): "more hypnotic-like".
No improvement in 2 weeks

Agrees to increase in dose (30 mg).
2 wks later: no sleep problem, energy returns, clear difference
Wants to stop medication but agrees to 5-month treatment

Arousals: part of depression

Case 4: 30-40 years

Janet, 36y/o lawyer.
Had head injury (women's hockey): can't concentrate (2 yrs).
Missed 2 court dates: Judge issues "Contempt of Court".
Referred by her council & family doctor.
Has had EEG, MRI: *Nil of note*
Neuropsychology: "*Non-specific defects*"

Sleep Consultation: some problems with sleep. No EDS

Sleep Study: Sunday

Study Start: 10 pm
SOL: 19 min
REM Latency: 87 min
Arousal Index: 48/hour
MSLT: not done

AHI: 2/hr
PLMS: <1/hr
Sleep Stages: Normal.
Slight ↓ REM & SWS

What would you do?

Case 4: 'Lawyer' continued

Trial of 8 wks of Zopiclone
Dramatic subjective improvement
Her lawyer phones to say "*Thanks*'.
Judge informed: Contempt of Court sanction withdrawn

Repeat Sleep Study performed: 7 weeks on Zopiclone
All features same,
Except: Arousal Index = 4 (formerly AI=48/hr)
Stopped medication: improvement endures

Arousals: "??Psychophysiological"

What about data from our sleep clinic?

629 Sleep Clinic patients:
overnight PSG & daytime testing (MSLT)

	Sleepiness			Fatigue	Alertness		Mood
	MSLT	**ESS**	**SSS**	**FS**	**ZOGIM-A**	**THAT**	**CES-D**
Arousal Index	-0.002	0.128	-0.046	-0.085	0.118	0.102	0.08
significance	p=0.95	p=0.001	p=0.3	p=0.03	p=0.003	p=0.01	0.04

Based on our data, there was no correlation between Arousal Index and measures of sleepiness, fatigue, alertness or mood.

Evidence of link between sleep fragmentation & EDS

"***Sleepy Girls***" by Jonathanin Bali

Sleep fragmentation & EDS

CORRELATION OF SLEEP PARAMETERS WITH DAYTIME SLEEP TENDENCY (DAILY MULTIPLE SLEEP LATENCY TEST SCORE)

Sleep Parameter	Correlation Coefficient	$p<$
Nocturnal Sleep Latency	.198	ns
Sleep Period Time	−.273	ns
Wakefulness After Sleep Onset	−.002	ns
Wakefulness After Final Arousal	.170	ns
Sleep Efficiency Index	−.125	ns
Total Sleep Time	−.140	ns
Stage 1 Time	−.270	ns
Stage 2 Time	−.019	ns
Stage 3 Time	−.025	ns
Stage 4 Time	−.114	ns
REM Time	.212	ns
Stage 1%	−.196	ns
Stage 2%	.082	ns
Stage 3%	−.029	ns
Stage 4%	−.126	ns
REM %	.247	ns
Number of Body Movements	−.199	ns
Stage 1 Shifts	−.309	ns
Wake Shifts	−.386	0.10
Transient Arousals	−.474	0.02
Transient Arousal Index	−.418	0.05
Respiration Events	−.491	0.02
Respiration Disturbance Index	−.407	0.05

24 male and female healthy & ambulatory subjects aged 63-86 years

Which PSG variable(s) are better predictors of EDS?

Arousals and respiration events were the **only** nocturnal variables significantly correlated with MSLT scores.

Increased transient arousals and respiratory events were associated with **greater sleepiness on the** MSLT

Carskadon et al. Neurobiol Aging. 1982

Sleep Fragmentation as a cause of EDS

Fragmented sleep is due to reoccurring episodes of EEGA triggered by various abnormalities during sleep

e.g., apnea/hypopnea events with OSA

leg movement events in PLMS.

OSA/PLMS

→ **Sympathetic Activation**

→ **EEG arousal**

→ **Sleep Fragmentation**

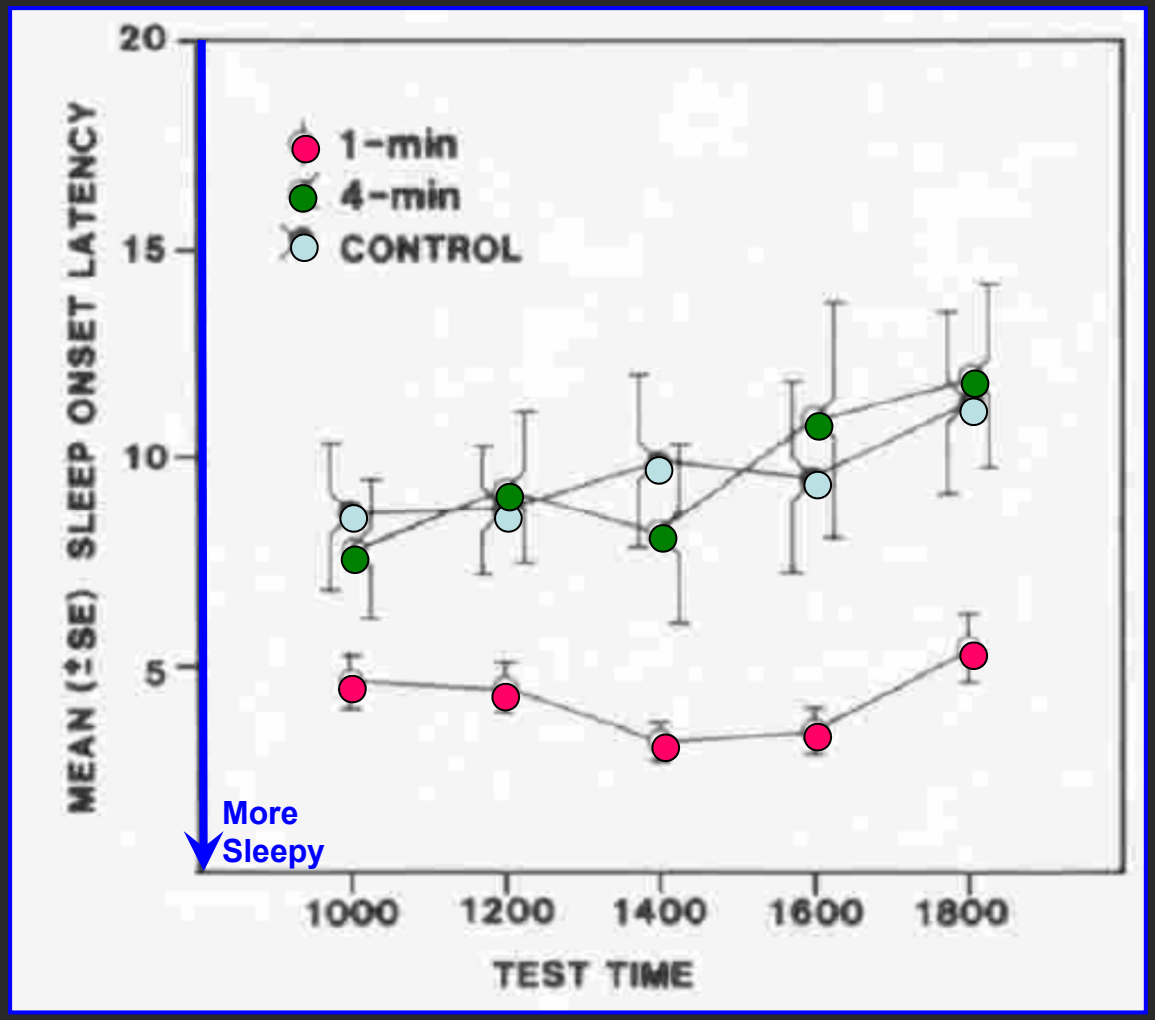
→ **EDS**

Sleep fragmentation is the predominant factor in causing EDS

- Although it may vary from one disease to another, sleep fragmentation has been found to lead to EDS & daytime fatigue.
- The contribution of sleep fragmentation to EDS is still under debate owing to the poor linear relationship between the number of micro-arousals and EDS as assessed subjectively or objectively [1].
- This may be related to individual susceptibility, circadian factors and other confounding factors such as stress axis activation.
- Interestingly enough, although sleep fragmentation only partially explains the variance of EDS or change in EDS after treatment, there is no difference according to the method used to assess sleep fragmentation [2].

Levy & Pepin, Sleep Med, 2003;
[1] Kingshott et al., Eur Respir J 1998
[2] Bennett et al., Am J Respir Crit Care 1999;159:1884–90.

Uninterrupted sleep is an essential determinant of the ability to remain awake during the daytime

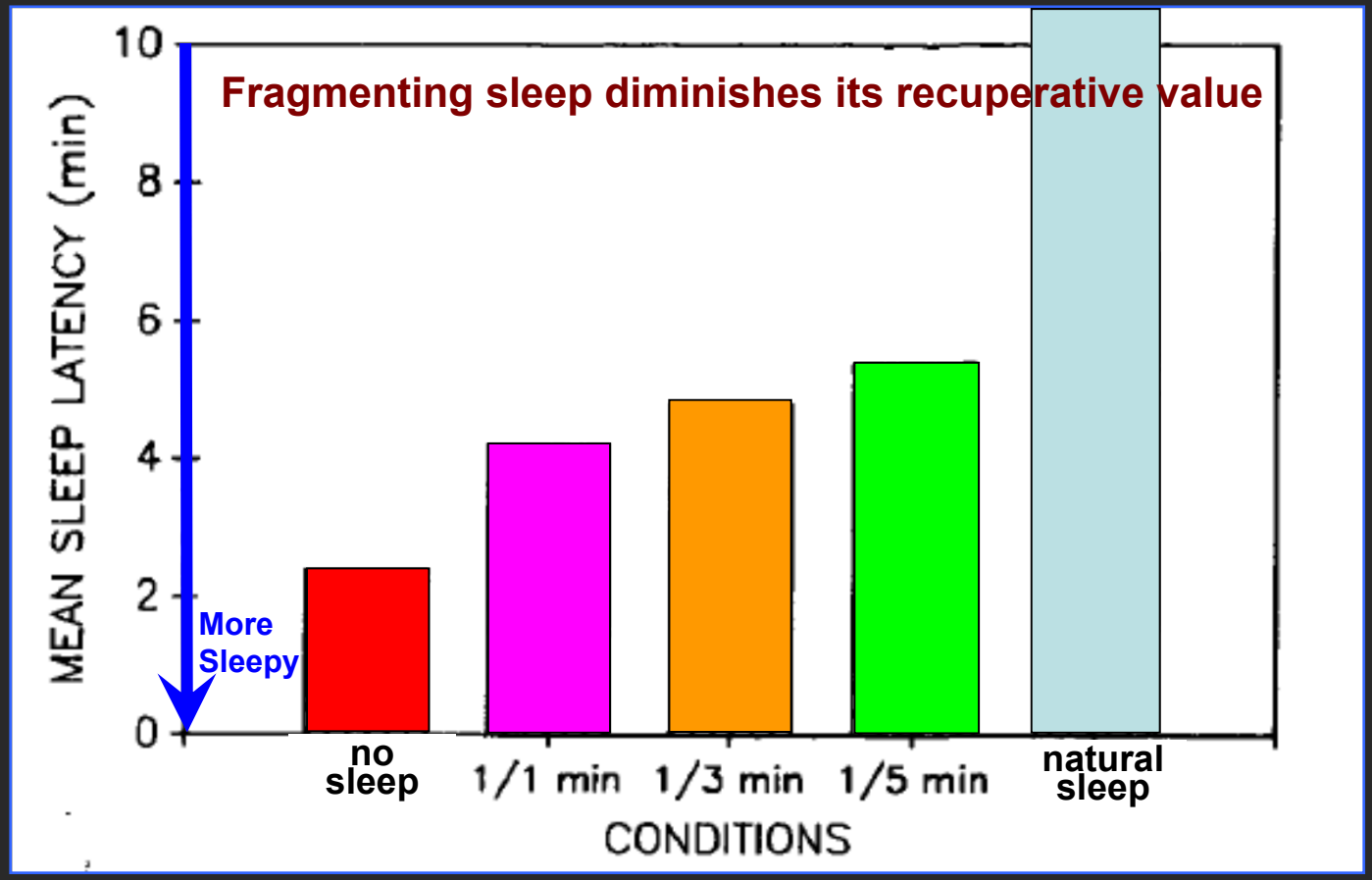


Effects of experimentally induced sleep fragmentation on sleep and sleepiness:

- once every 4 mins
- once every minute

Magee et al., Psychophysiology, 1987

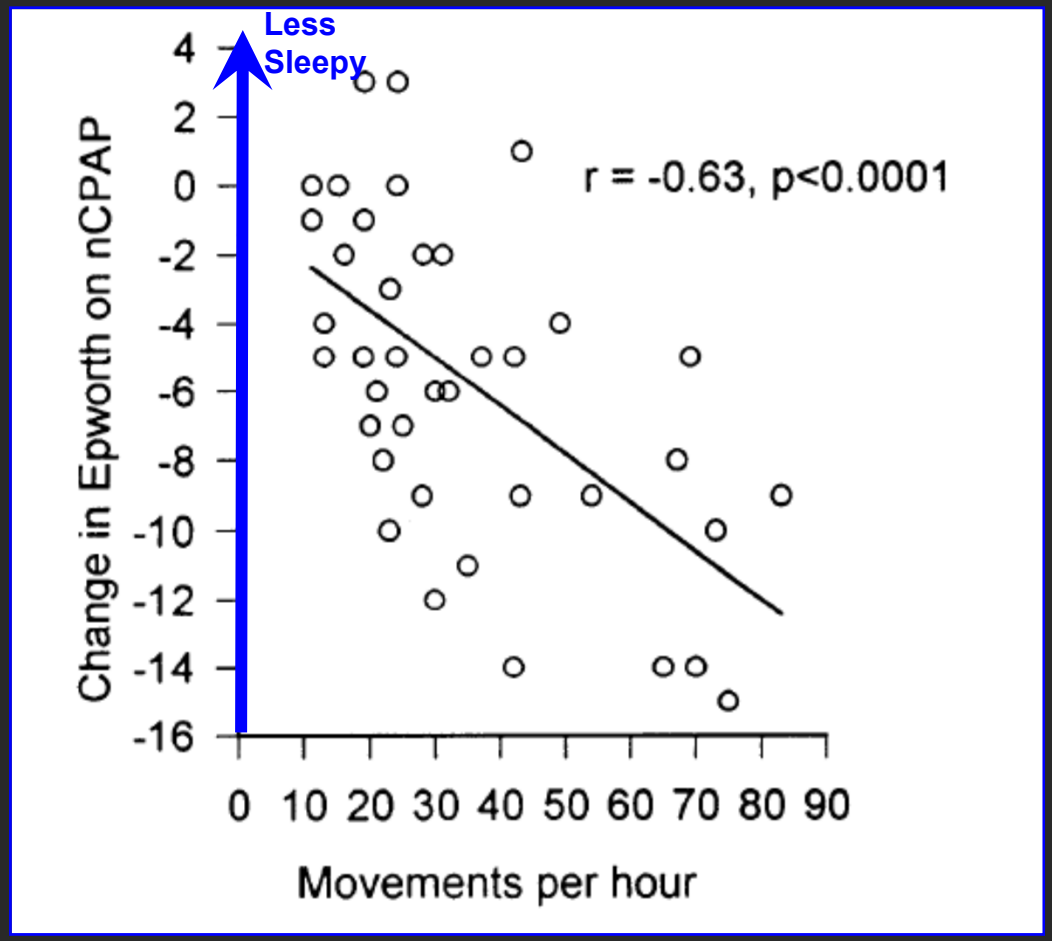
"Dose-Response Effect" of increasing degrees of sleep fragmentation on EDS



Tones (90 dB) administered during sleep at rates of 1/1min, 1/3min, 1/5 min, or with total sleep deprivation or natural sleep

Levine et al., Sleep, 1987

The converse holds: A reduction in arousals results in less EDS



CPAP use reduces the number of movement-induced arousals which in turn is significantly related to a **reduction in EDS**

Bennett et al., Am J Respir Crit Care Med, 1998

Neurobiology of sleep fragmentation as relates to EDS

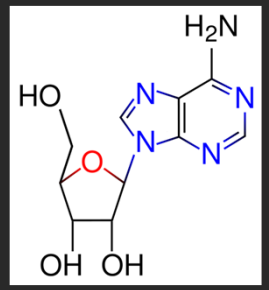
The Wind moved over my shoulder and tickled my ears. "You sleep, you dream of earth goddess art and exotic days?" The Wind did whisper my fancy.

Artist: Kathy Ostman-Magnusen

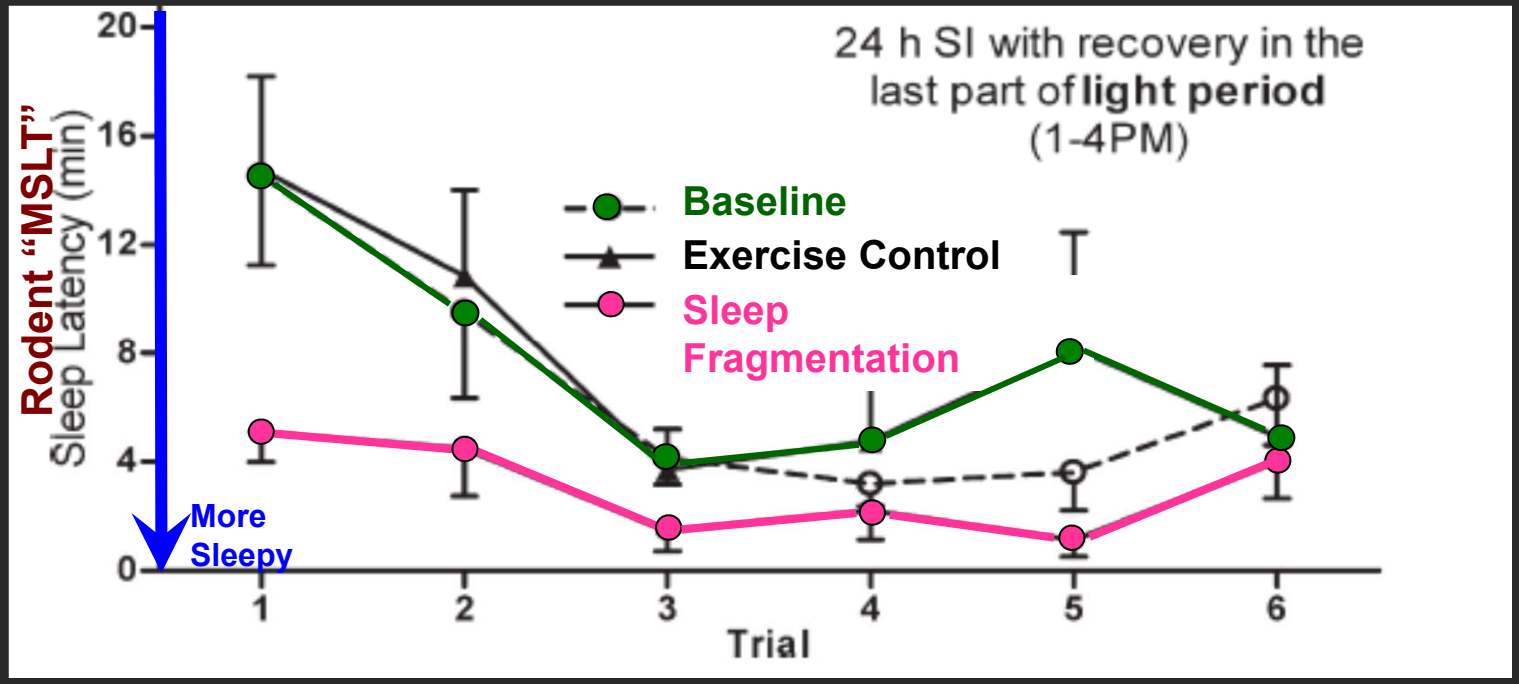
Neurobiology of sleep fragmentation as relates to EDS: Adenosine

Adenosine (AD), an inhibitory neuromodulator, is proposed to be an endogenous sleep factor

Systemic and intracerebral injections of AD have been shown to increase sleep, while AD antagonists (eg, caffeine) increase arousal.



Rodent model of sleep fragmentation & EDS



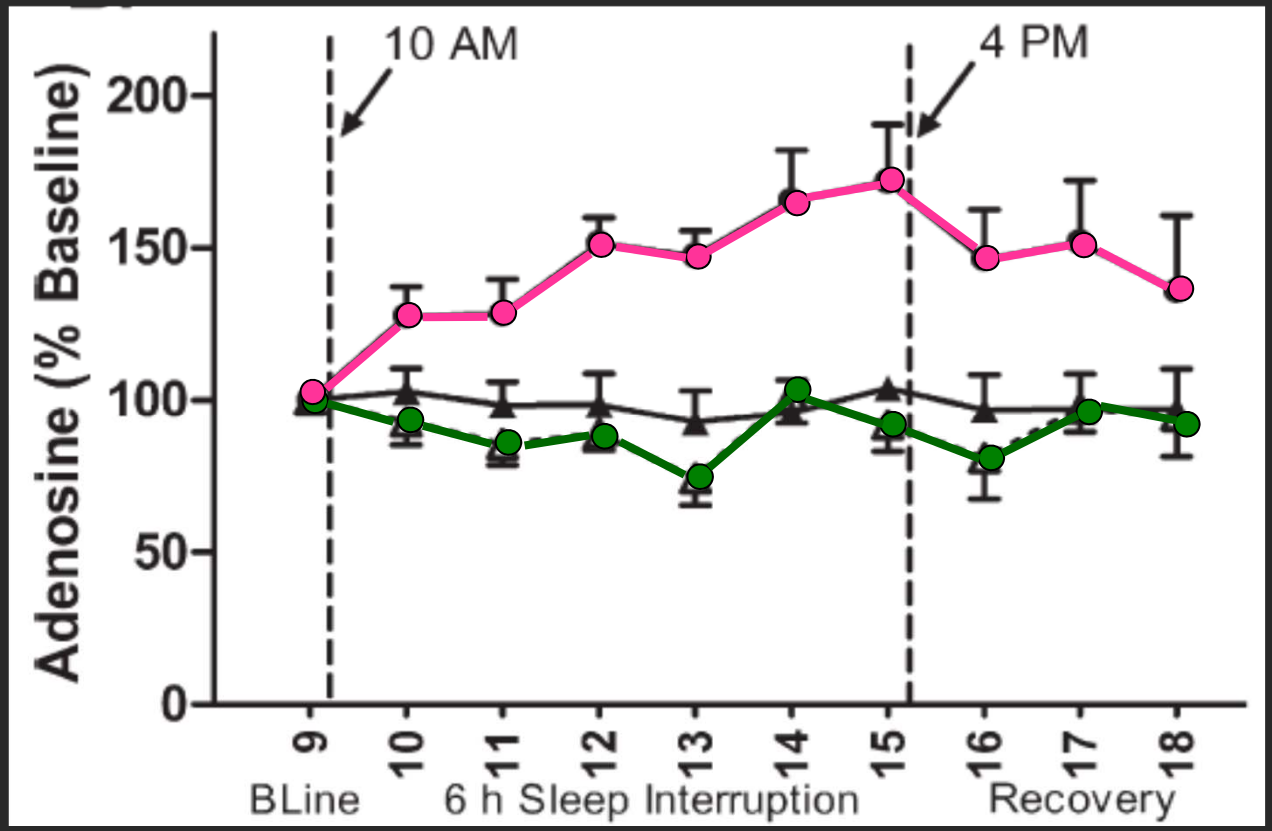
Rats lived in a normal light-dark cycle in a modified treadmill cage with a movable horizontal belt in the floor.

For Sleep Fragmentation, the treadmill ran at a slow speed of 0.02 m/s for 30 s (30 s on), followed by no treadmill activity for 90 s (90 s off), producing 30 interruptions of sleep per hour.

Control: an exercise group of different rats were exposed to treadmill movement for 10 min on, followed by 30 min off to produce a comparable overall amount of movement/exercise.

Mckenna et al., Neuroscience, 2007

Sleep Fragmentation & Adenosine levels



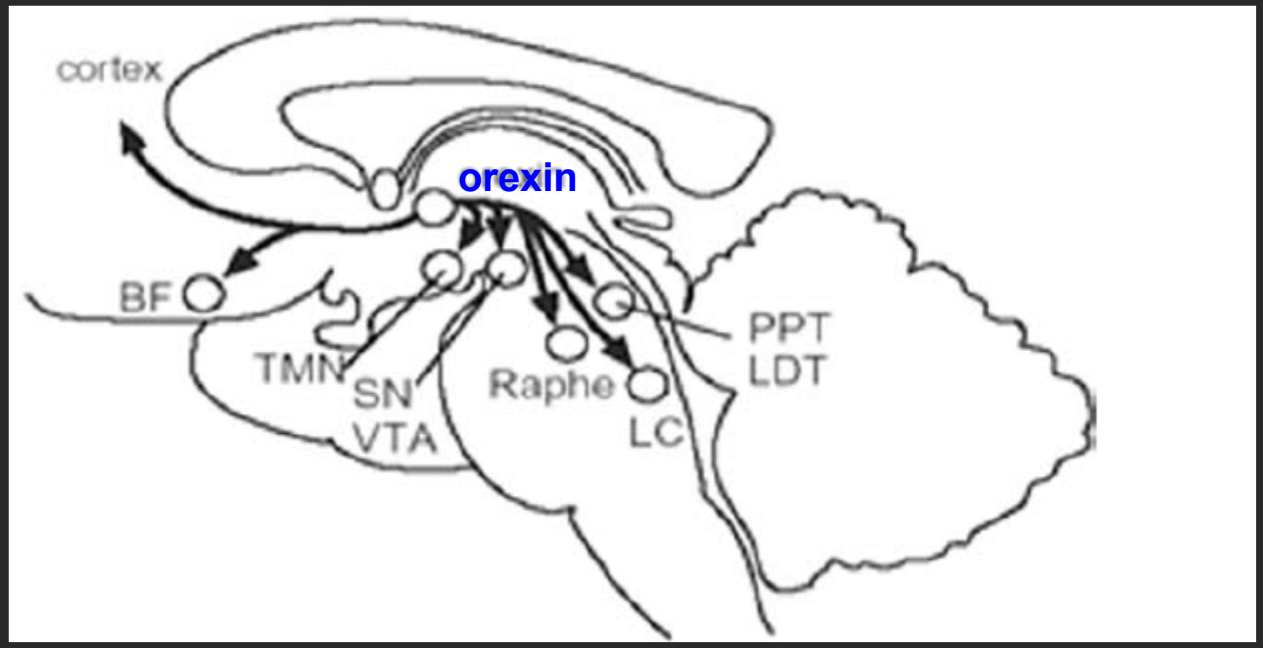
Extracellular basal forebrain **Adenosine** levels were significantly elevated during Sleep Fragmentation compared with control groups. (Irrespective of whether 6 h of SI was terminated at the end of the light period or during the light period (shown above).

Mckenna et al., Neuroscience, 2007

Neurobiology of sleep fragmentation as relates to EDS: Orexin

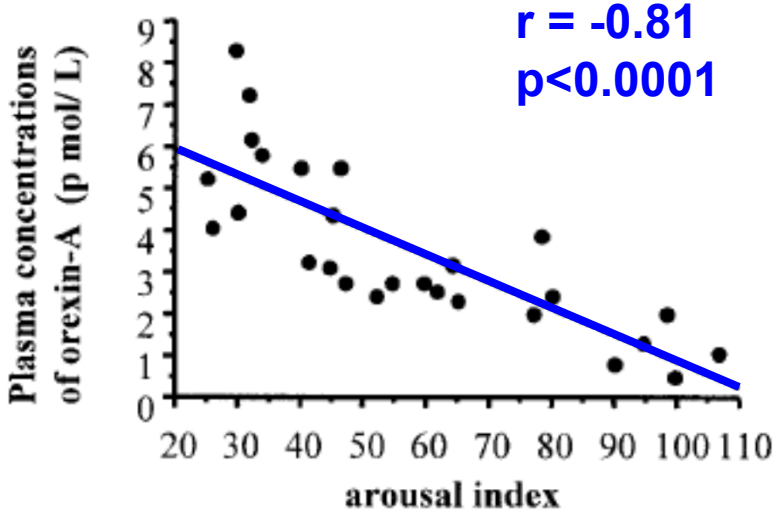
Orexin neurons have predominately excitatory effects on postsynaptic targets.

Important role in ascending neural regulation of wakefulness

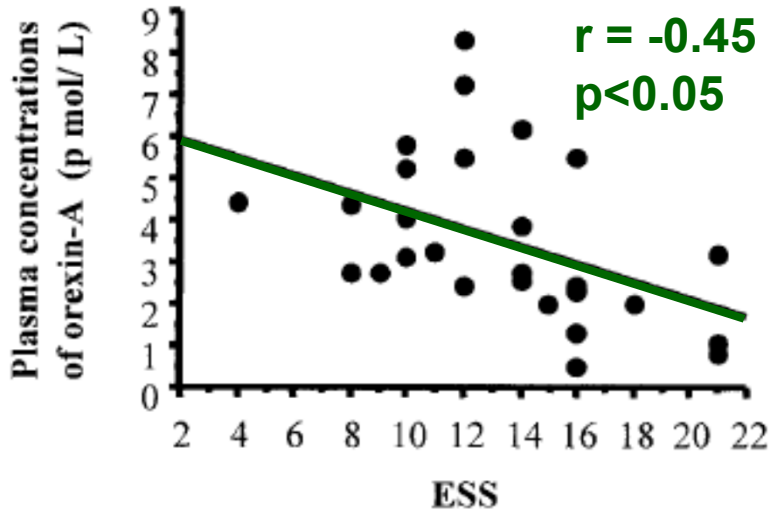


Orexin, Sleep Fragmentation & ESS

Arousal Index



Epworth Sleepiness Scale



27 sleep clinic patients (in their 50's) diagnosed with OSA and compliant with CPAP treatment for 3-6 mths.

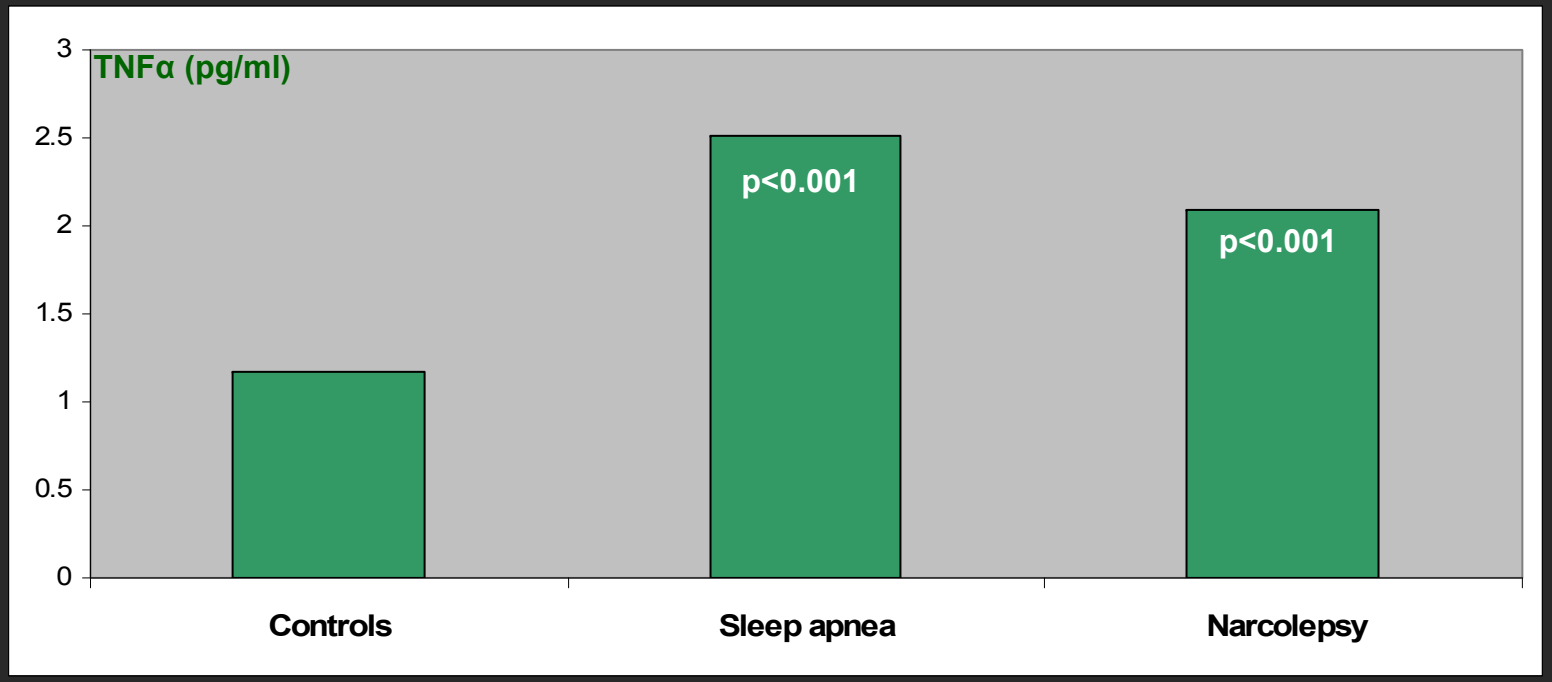
Plasma IR-orexin-A concentrations were found to be significantly and inversely correlated with the Arousal Index and scores on the ESS.

Sakurai et al., Chest, 2005

Neurobiology of sleep fragmentation as relates to EDS: TNFα

TNFα is a pro-inflammatory cytokine that functions in host defense and mediates the pathogenesis of a number of disease processes

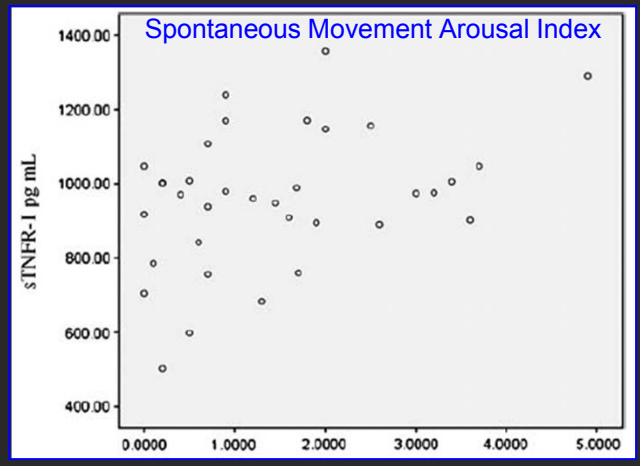
TNFα is significantly increased in disorders of excessive daytime sleepiness such as sleep apnea and narcolepsy

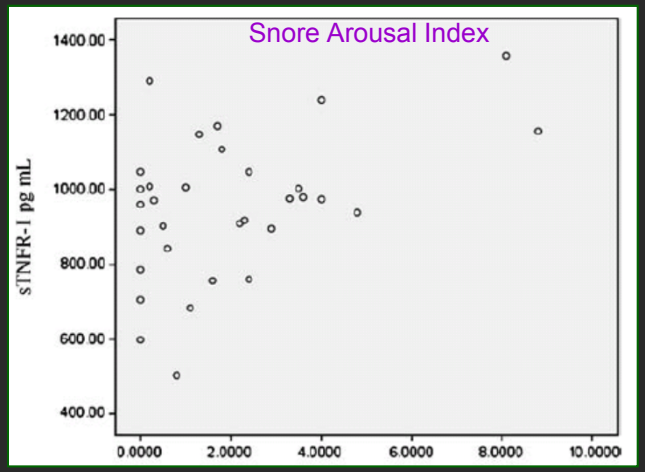


Vgontzas, Journal of Clinical Endocrinology and Metabolism, 1997

TNFα & Arousals

	sTNF-RI	
% light sleep (stage S1)	0.053	
% light sleep (stage S2)	0.093	
% deep sleep (stage S3 + S4)	0.124	
% REM Sleep	0.083	
AHI	0.169	
AI	0.301	
ODI	0.265	
Total arousal index	0.170	
Snore arousal index	0.449	p<0.01
Spont cortical arousal index	0.220	p<0.05
Resp cortical arousal index	0.072	
Spont movement arousal index	0.378	p<0.01
Resp movement arousal index	0.224	
Periodic limb movement arousal index	0.460	p<0.01





sTNF-RI (a soluble form of TNFα) is significantly associated with indices of arousal (snore arousals, spontaneous movement arousals, PLM arousals).

sTNF-RI is NOT significantly associated with apnea severity or desaturation indices.

Yue et al., Sleep Breath 2009)

Neurochemical link between sleep fragmentation and sleepiness:

More candidates to be explored…