Overview

I. Normal sleep

II. Recording sleep

III. Effects of sleep on epilepsy

a. Temporal association between sleep and epilepsy

b. Effects of sleep deprivation on epilepsy

IV. Sleep-wake disorders in epilepsy patients

V. Effects of epilepsy on sleep

a. Effects of epilepsy on sleep architecture

b. Effects of antipeileptic drugs on sleep

VI. Differential diagnosis of nocturnal paroxysmal events

What is sleep?

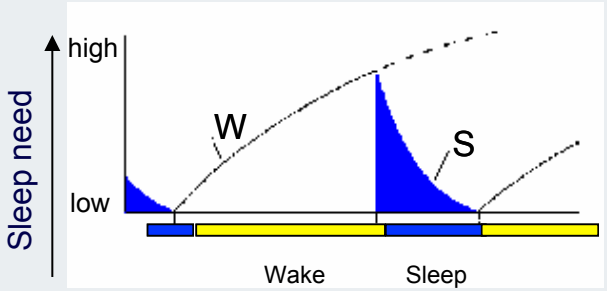
- Sleep is defined behaviorally by 4 criteria:
  - reduced motor activity
  - decreased response to activity
  - stereotypic postures
  - reversibility
- Two major processes regulate sleep: circadian and homeostatic
- Sleep is organized in stages and cycles

Sleep regulation

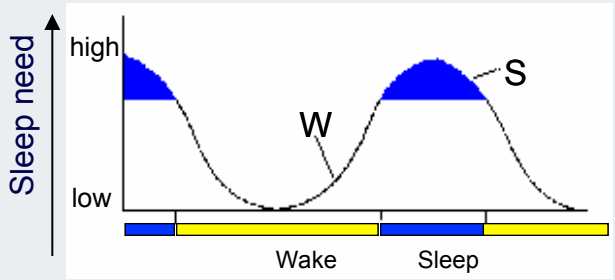
The two process model of sleep

Homeostatic process (time-dependant):

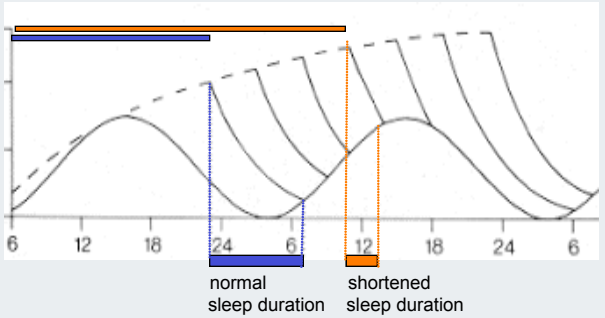
The longer we stay awake, the bigger the sleep need



Circadian process (internal clock)



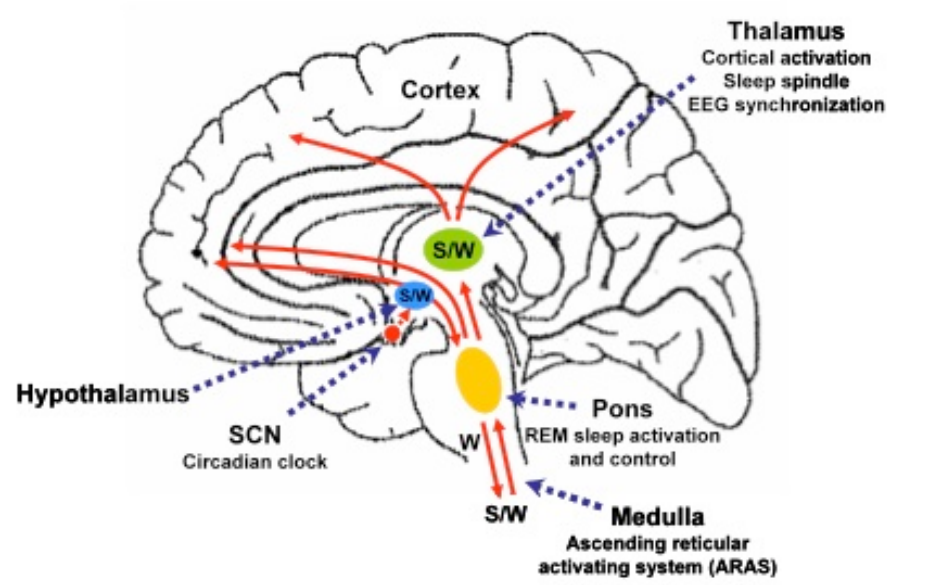
Interaction between the two processes



Adapted from Borbély, 1982

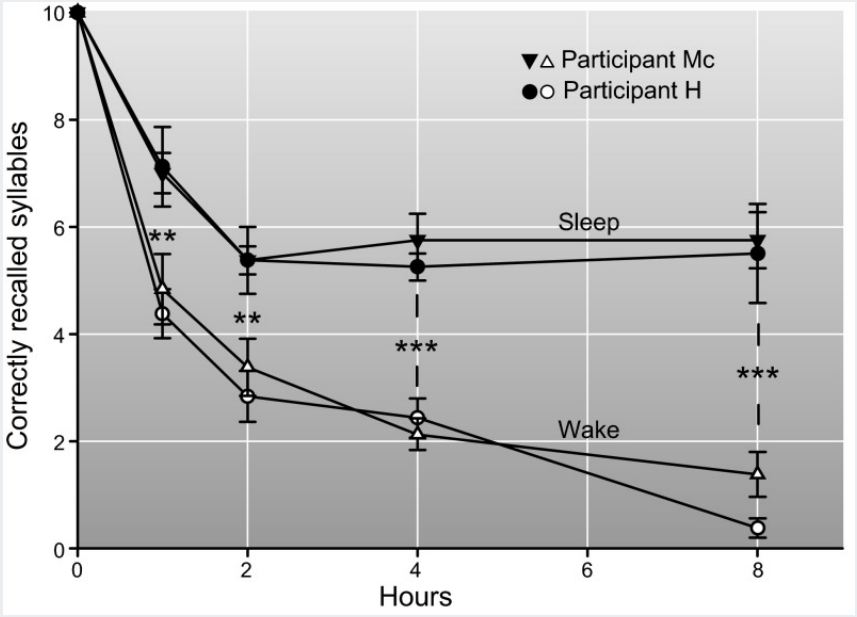
Sleep regulation

Important structures in sleep-wake regulation



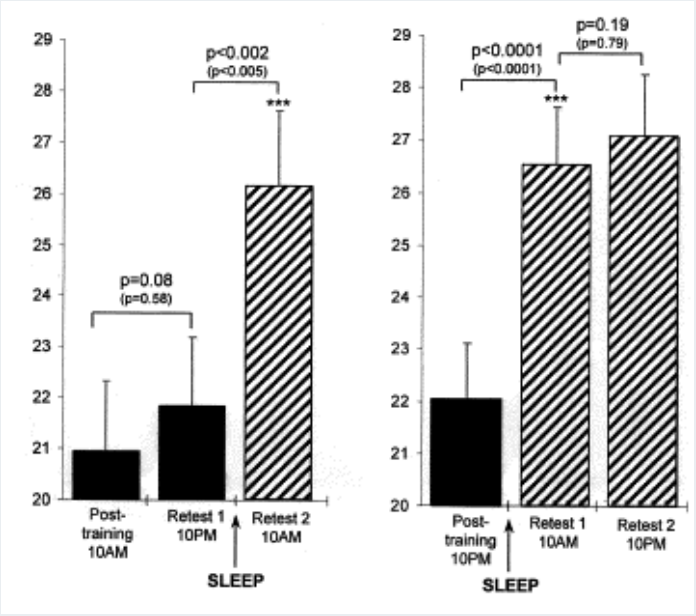
Function of sleep

The role of sleep in remembering



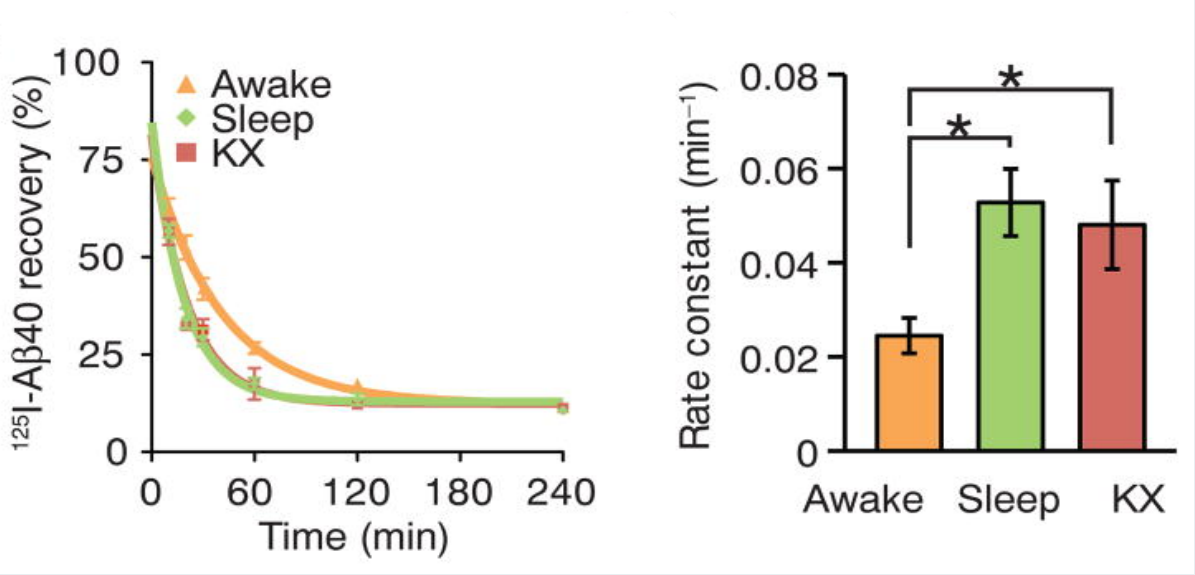
Jenkins & Dallenbach, 1924

Practice with sleep makes perfect: sleep-dependent motor skill learning



Walker et al., 2002

Function of sleep

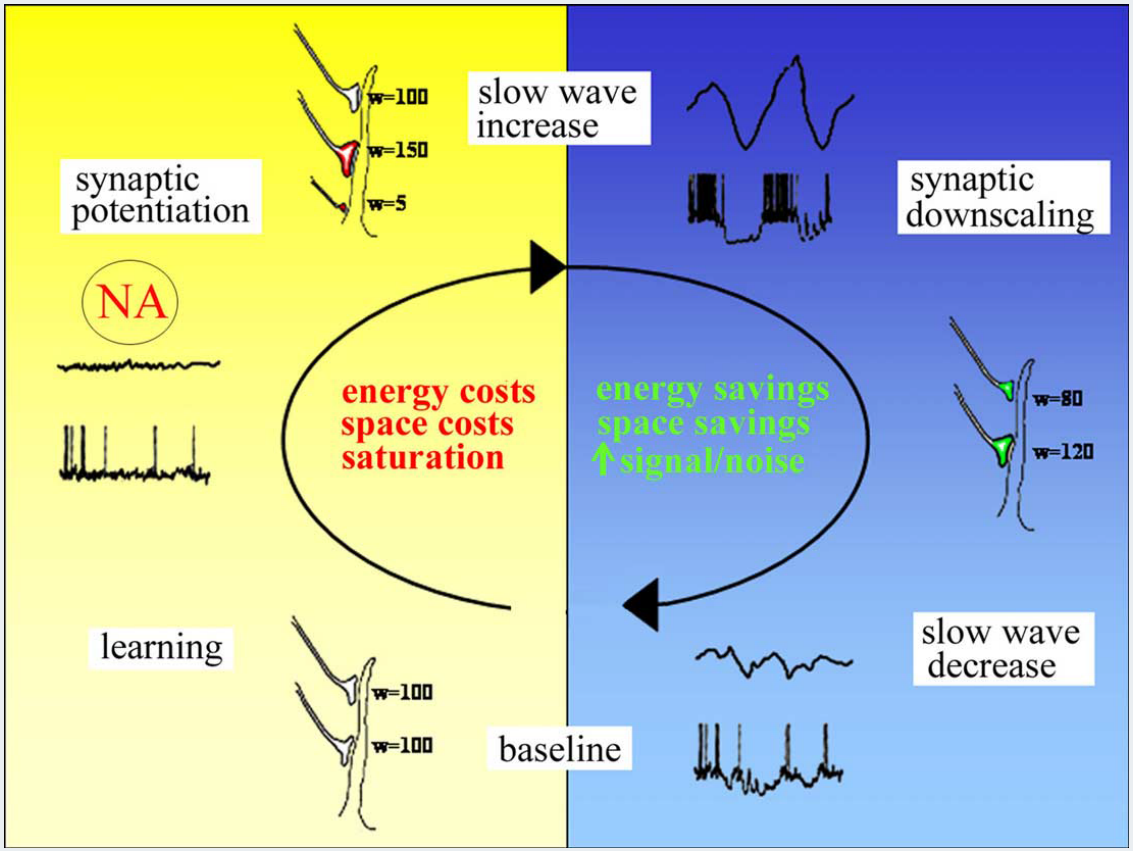


Xie et al., 2013

Natural sleep or anesthesia are associated with enhanced removal of potentially neurotoxic waste products that accumulate in the awake central nervous system.

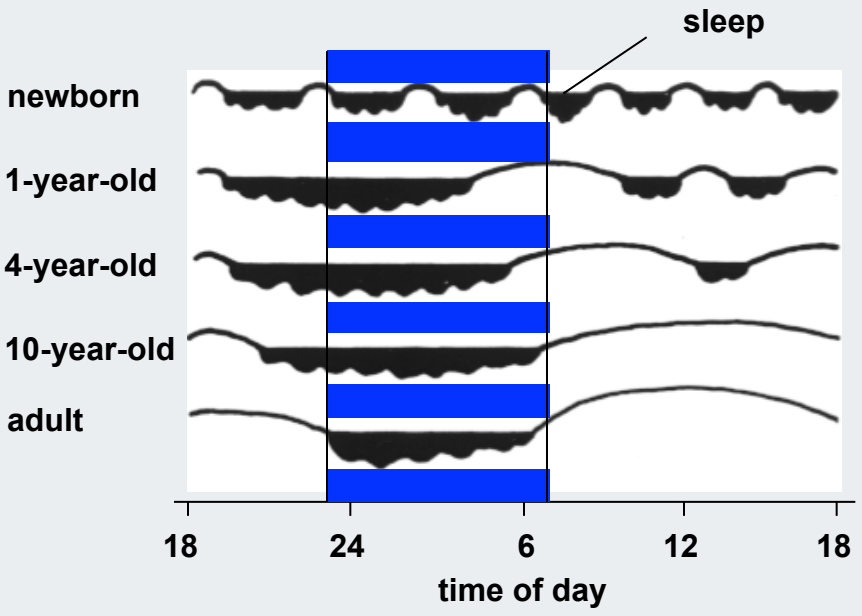
Function of sleep

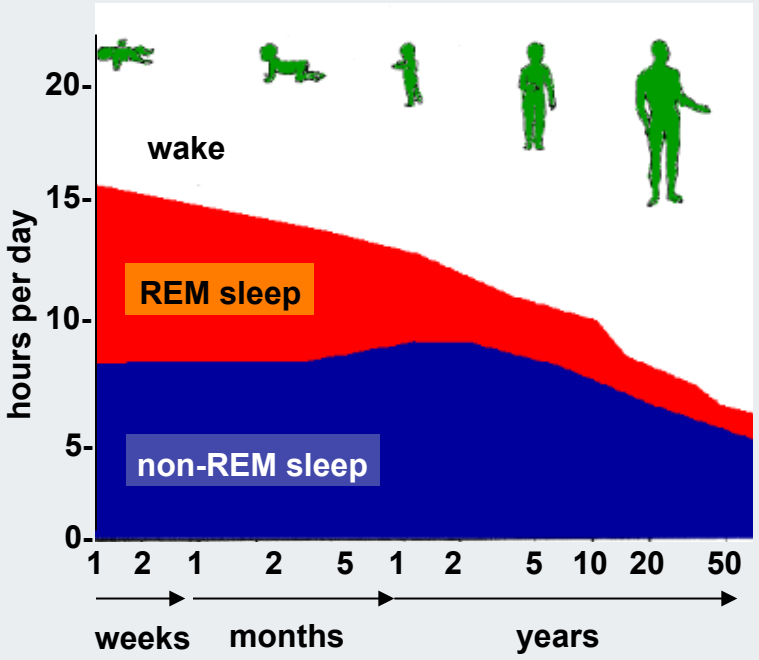
Synaptic homeostatic hypothesis



Tononi & Cirelli, 2006

Sleep profile and need changes with age





from Borbély, 1984

Polysomnography

Measures:

Brain activity = EEG

Muscle activity (on the chin)

Eye movements

Breathing

Heart activity = EKG

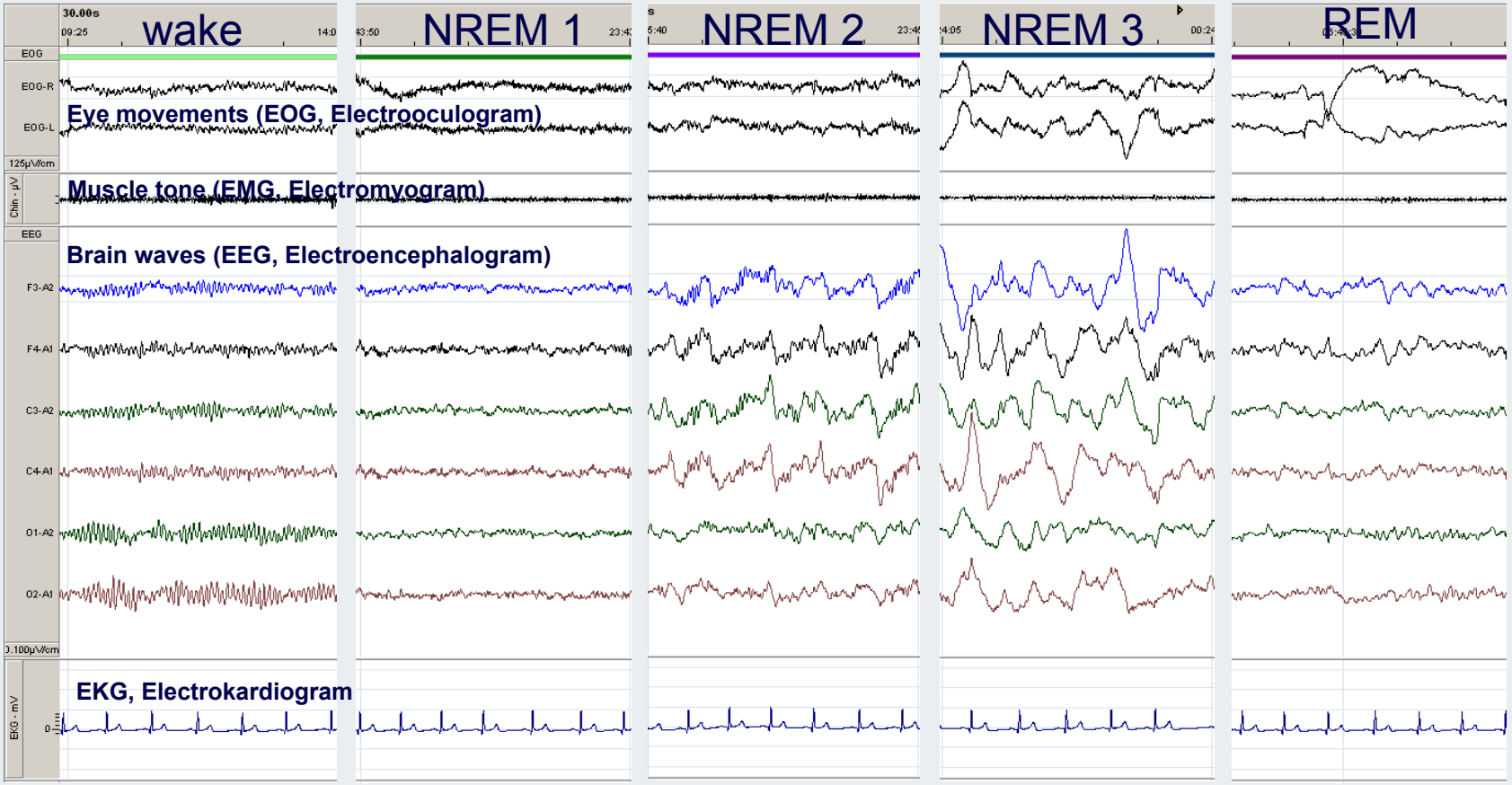
Leg movements

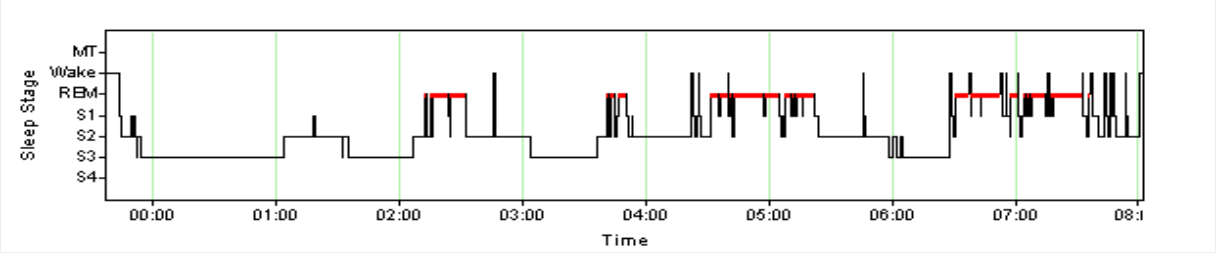
Snoring sensor

Oxygenation

Video – for behavioral peculiarities

II. Recording sleep





a. Temporal association between sleep and epilepsy

- Aristotle observed epileptic seizures in sleep *(Temkin, 1971)*
- 2/3 of seizures occur between 8pm and 8am *(Féré, 1880)*
- Of 850 institutionalized patients with seizures *(Gowers, 1885)*
  - 21% only at night,
  - 42% only during the day
  - 37% either during the night or day
- Peaks of seizures occur in response to falling asleep and awakening *(Langdon-Down & Brain, 1929)*
- In sleep-related epilepsy, diurnal seizures, if present, in the first 2 years *(Gibberd & Bateson, 1974, D'Alessandro et al., 2004)*

a. Temporal association between sleep and epilepsy

Sleep and Awakening Epilepsies
Sleep epilepsies
Benign childhood epilepsy with centro-temporal spikes (BECTS)
Early-onset benign childhood occipital epilepsy (EOCOE)
Frontal lobe epilepsy (FLE)
Autosomal dominant nocturnal frontal lobe epilepsy (ADFLE)
Electrical status epilepticus during sleep (ESES)
Landau–Kleffner syndrome (LKS)
Awakening epilepsies
Juvenile myoclonic epilepsy
Absence epilepsy
Epilepsy with grand mal seizures on awakening

Rocamora et al., 2008

a. Temporal association between sleep and epilepsy

Clinical features:

- Brief (<2 minutes) seizures with stereotyped motor patterns within individuals and abrupt onset and offset
- The most common clinical expression consists of “hypermotor” events
- Seizures of SHE occur predominantly during sleep; however, seizures during wakefulness may also occur

Electroclinical features:

- Interictal and ictal EEG may be normal
- Prolonged video-EEG recording is the best diagnostic test but, if negative, does not rule out the diagnosis as seizures may not be recorded and interictal EEG may be normal
- Sleep-related hypermotor seizures may arise from various frontal as well as from extrafrontal areas

Tinuper et al., 2016

a. Temporal association between sleep and epilepsy

Sleep related hypermotor epilepsy (SHE)

Diagnostic certainty

- Diagnosis of SHE is primarily based on clinical history. The absence of clear interictal and ictal EEG correlates, both during wakefulness and sleep, does not exclude the diagnosis of SHE
- Certainty of diagnosis can be categorized into 3 levels:
  - witnessed (possible) SHE,
  - Videodocumented (clinical) SHE,
  - and video-EEG documented (confirmed) SHE.

Tinuper et al., 2016

a. Temporal association between sleep and epilepsy:

Sleep stage and epileptic seizures

Sleep promotes initiation and propagation in partial seizures

- Partial seizures, occuring during sleep *(Herman, 2001; Minecan, 2002)*:
  - 61-68% in N2
  - 20-23% in N1
  - 9-14% in N3
  - only 0-5% in REM

Stage N2 promotes secondary generalisation in temporal and occipotoparietal but not frontal lobe seizures

a. Temporal association between sleep and epilepsy

Effect of sleep stage on interictal and ictal epileptiform discharges

Vaughn & D'Cruz, 2004

Effect of Sleep Stage on Interictal and Ictal Discharges

NREM Sleep Seizure Promotion	REM Sleep Seizure Inhibition
Synchronization of EEG	Desynchronization of EEG
More frequent interictal discharges	Less frequent interictal discharges
Wider spread of interictal discharges	Greater localization of interictal discharges
Increase likelihood of seizures	Infrequent seizures
Greatest potential for epileptogenesis	Greater REM sleep time results in fewer seizures
	Least potential for epileptogenesis

b. Effects of sleep deprivation on epilepsy

Effects of sleep deprivation on seizures

- Sleep deprivation as a seizure precipitant, especially in awakening epilepsy *(e.g. Janz, 1974)*
- 71 patients with partial epilepsy: seizure probability – hours asleep *(Haut et al., 2007)*
- 14 patients with temporal lobe epilepsy and sleep diary for 2 years: night sleep duration correlated with seizure frequency *(Rajna & Veres, 1993)*

b. Effects of sleep deprivation on epilepsy

Effects of sleep deprivation on interictal epileptiform discharges

- Sleep vs. sleep deprivation
- Longer recording
- Repeated recording
- Increased cortical excitability

Sleep deprivation ⟶ epileptic seizures

Sleep ⟶ epileptic discharges

Epilepsy ⇆ Sleep-wake disturbances

- Sleep diturbances more common in epilepsy *(de Weerd et al., 2004, Khatami et al., 2006)*
- Excessive daytime sleepiness: in 11 up to 50%
- Obstructive sleep apnea: in 10% up to 65%
- Treating sleep apnea improves seizure control?
- Restless legs syndrome: in 10% up to 33%
- Parasomnias with variable frequency
- Sleep-wake disorders affect quality of life in epilepsy patients

a. Effects of epilepsy on sleep architecture

- ⇧ Sleep latency
- ⇧ REM latency
- ⇧ WASO
- ⇧ Arousals/awakenings/stage shifts
- ⇧ NREM1

- ⇩ Sleep efficiency
- ⇩ REM sleep duration
- ⇩ SWS duration

- Found also in the absence of seizures
- In partial and idiopathic generalized epilepsies (in the latter group inconsistent results)
- More often in TLE than in FLE *(Crespel et al., 2000)*
- Treating epilepsy improves sleep architecture *(Touchon et al., 1991)*

b. Effects of antipeileptic drugs on sleep architecture

	Effects on sleep					
	Sleep efficiency	Sleep latency	Stage I	Stage II	Stage III	REM
Phenobarbital	↑	↓	–	↑	0	↓
Phenytoin	0	↓	↑	↑	↓	0 or ↓
Carbamazepine	0	0	0	0	0	0
Valproate	–	0	↑	↓	0	0
Ethosuximide	–	–	↑	–	↓	–
Gabapentin	0	0	0	0	↑	↑
Lamotrigine	0	0[b]	0	↑	↓	↑
Topiramate	0	↓	0	0	0	0
Tiagabine	–	–	–	–	↑	–
Levetiracetam	–	–	–	–	↑	–
Pregabalin	↑	–	–	–	↑	–

Eriksson, 2011

c. Effects of antipeileptic drugs on sleep disturbances

	Effects on sleep disorders	
	Improves/treats	Worsens
Phenobarbital	Sleep-onset insomnia	OSA
Phenytoin	None known	None known
Carbamazepine	RLS	RLS
Valproate	None known	OSA[a]
Ethosuximide	None known	None known
Gabapentin	RLS	OSA[a]
Lamotrigine	None known	None known
Topiramate	OSA[a]	None known
Tiagabine	Insomnia	None known
Levetiracetam	None known	None known
Pregabalin	None known	OSA[a]

Eriksson, 2011

Paroxysmal behavioral events in sleep

- Sleep-related epileptic seizures
- NREM parasomnia (confusional arousal, sleep terror, sleepwalking)
- REM parasomnia (REM-sleep behavior disorder)
- Paroxysmal hypnogenic dystonia
- Nightmare disorder
- Sleep-related dissociative disorder
- Sleep-related panic disorder
- Gastroesophageal reflux
- Sleep-realted rhythmic movement disorder
- Catathrenia

Parasomnias

- Undesirable physical events or experiences, that occur during entry into sleep, within sleep or during arousals from sleep

- They can be: abnormal sleep related movements, behaviors, emotions, perceptions, dreaming and autonomic nervous system functions

- Their diagnosis is important because of the consecutive sleep fragmentation and risk of injuries

- The patient and his/hers bed partner can be affected

Parasomnias types

1. NREM parasomnia: confusional arousal, pavor nocturnus, sleepwalking
2. REM parasomnia: REM sleep behavior disorder: RBD
3. Overlap parasomnia

Sleepwalking

- Complex sleep-associated behaviors with locomotion, mental confusion and amnesia for the episode; injuries are common
- Epidemiologie:
  - In children up to 10%
  - In adults 2-4%,
  - yet “de novo” in adults in only 0.6%

Hublin C et al., Neurology, 1997

Sleepwalking

- Etiology

- genetic predisposition - association with HLA-DQB1*04 und HLA-DQB1*05

- Triggers

- medication: Zolpidem, Lithium, Bupropion, Mirtazapin

- sleep deprivation

- sleep disorders with arousals, e.g. sleep apnea

- pregnancy

- stress

Sleepwalking: clinical symptoms

- Occurres in the first half of the night
- Sitting up, standing up or walking
- Desorientation
- Often eyes open
- Aggressive behavior is possible
- Possible injuries
- Amnesia for the episode

Sleepwalking: diagnosis

- History
  - typically since childhood
  - positive family history
  - typical clinical symptoms
- Polysomnography
  - out of an arousal from deep sleep
  - sometimes synchronous delta-activity before the episode
  - often delta-theta during the episode in spite of open eyes

Sleepwalking: therapy

- Secure environment

- Cognitive behavioral therapy
- low dose benzodiazepines
- sedating antidepressants

} evidence weak

REM sleep behavior disorder (RBD)

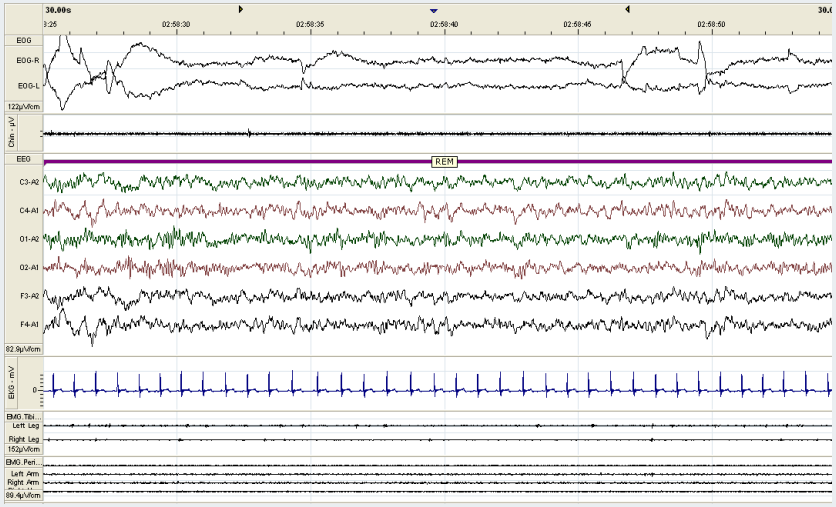
- Characterized by the loss of muscle atonia, normally observed in REM sleep, that can lead to dream enactment behavior
- Rare in healthy adults, 0.5% (Ohayon et all, 1997)
- Very common in Parkinson's diasease, up to 50% *(Eisensehr et al., J Neurol Sci. 2001, Yoritaka et al., Eur Neurol 2009)*
- Can precede the motor symptoms in Parkinson's diesase *(Schenck et al., Neurology 1996)*
- Risk for a neurodegenerative disease in idiopathic RBD *(Postuma et al, 2009):*

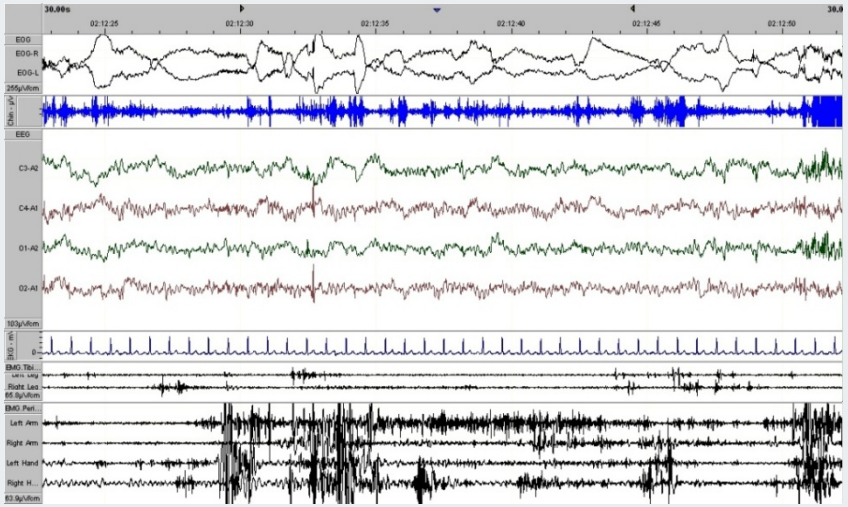
  - 5-year risk: 17.7%
  - 10-year risk: 40.6%
  - 12-year risk: 52.4%.

REM sleep behavior disorder (RBD): clinical characteristics

- Animated, threatening dreams, leading to aggressive behavior: hitting, kicking, grumbling, but also gesticulating, laughing, crying
- Often serious injuries (self- or bedpartner)
- Occurrs usually in the last third of the night
- Can be associated with hallucinations, cognitive impairment *(Sinforiani et al. Mov Disord 2008)*, vegetative symptoms *(Postuma et al., Mov disord, 2008)*
- Trigger factors: antidepressants, alcohol or alcohol withdrawal

REM sleep behavior disorder (RBD): polysomnography





REM sleep behavior disorder (RBD): therapy

- First choice:

Clonazepam 0,5–1 mg/d (cave: Exacerbation of sleep apnea)

- Second choice:

Melatonin 3 mg/d

L-Dopa 200 mg/d

Carbamazepin 200–400 mg/d

Secure environment

NREM Parasomnia and nocturnal frontal lobe epilepsy (NFLE)

Features strongly favoring parasomnias
Yawning
Scratching and prominent nose-rubbing
Rolling over in bed
Internal or external trigger (noise, cough, snore)
Waxing and waning pattern
Physical or verbal interaction
Sobbing, sad emotional behavior
Indistinct offset
Failure to fully arouse after event with complex behavior
Prolonged duration (>2 min)
Discordance between severity and duration of *reported* event and *recorded* event

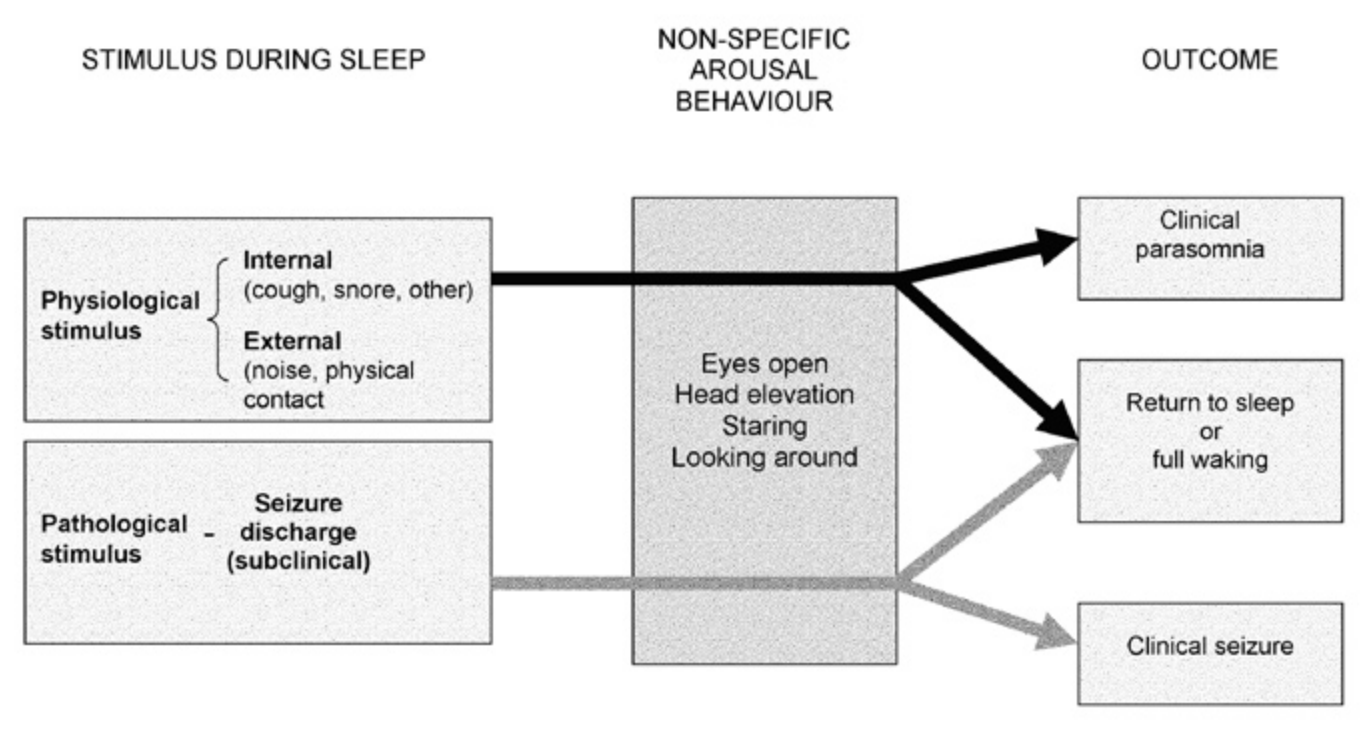
Derry et al., 2009

An overlap between parasomnia and NFLE has been suggested

Features moderately favoring parasomnias
Tremor/trembling
Myoclonic jerks
Coughing
Semipurposeful behaviors, fumbling, manipulation of nearby objects
Variability/absence of stereotypy
No events recorded on first night of monitoring
Few events recorded in total (less than 3)

Features which do *not* discriminate between parasomnias and NFLE
Brevity
Sitting
Standing or walking
Preceding 'normal' arousal
Brief arousals (up to 10 s) without definite semiological features of epilepsy
Fearful emotional behavior

NREM Parasomnia and NFLE: the role of arousal



Derry et al., 2009

Discussion

- Sleep and epilepsy are mutually interrelated
- Sleep, arousals from sleep and sleep deprivation can be epileptogenic
- Sleep disorders are common in epilepsy patients
- Sleep fragmentation due to sleep disorders can worsen seizure frequency
- Epilepsy can
  - worsen sleep architecture/ cause sleep complaints
- Epilepsy treatment can
  - both worsen and improve/relieve them

Discussion

- Differential diagnosis of nocturnal paroxysmal events is difficult
- Differentiating on clinical features is unreliable
- Gold standard for the diagnosis:
  - 10/20 polysomnography or long-term video-EEG recording

Thank you for your attention!