



5th Congress of the European Academy of Neurology

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Teaching Course 8

**Medical management issues of dementia - Role of the
neurologist (Level 2)**

Sleep in dementia

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Sleep disorders in dementia

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Conflict of Interest

- **In relation to this presentation and manuscript:**

- the Author has no conflict of interest in relation to this manuscript.
- the Author serves as medical consultant to: UCB Pharma, Jazz Pharma, Janssen Pharma, Boioprojet Pharma
- the Author is in the Advisory Board of: UCB Pharma, Jazz Pharma, Janssen Pharma, Boioprojet Pharma
- the Author received speaker's honoraria from: UCB Pharma, Jazz Pharma, Janssen Pharma, Boioprojet Pharma

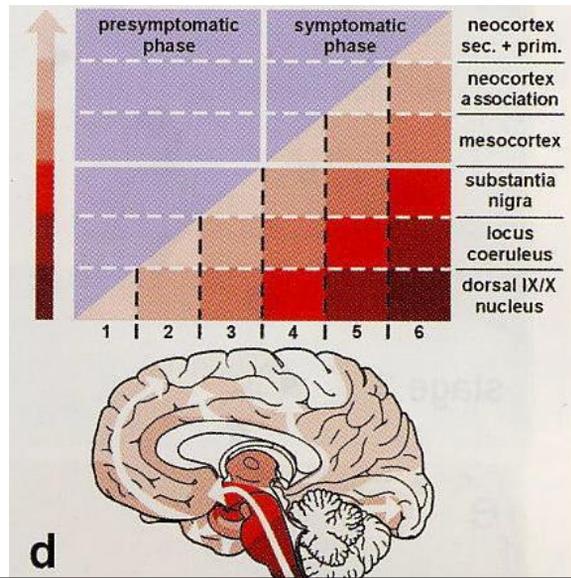
Learning objectives

- Sleep in dementia
- Comorbidity
- Sleep and memory
- Pathophysiology
- Predictors for dementia from sleep disturbance
- Diagnostic tools
- Therapies for dementia by treating sleep disorders

AD

- Aggregation of amyloid- β starts 20 years prior to onset of AD
- Progression results from age, genetic and environmental factors (i.e. exercise, diet, sleep...)
- Spreading of amyloid- β starts in the entorhinal cortex, goes to the hippocampus and the temporal lobe (Braak 1991)
- These structures are essential for memory consolidation
- Memory consolidation is mediated by sleep
- A- β has a diurnal fluctuation (high during wake, low during sleep)

Braak model of neurodegeneration (Braak 1988)



Factors contributing to impaired cognitive function

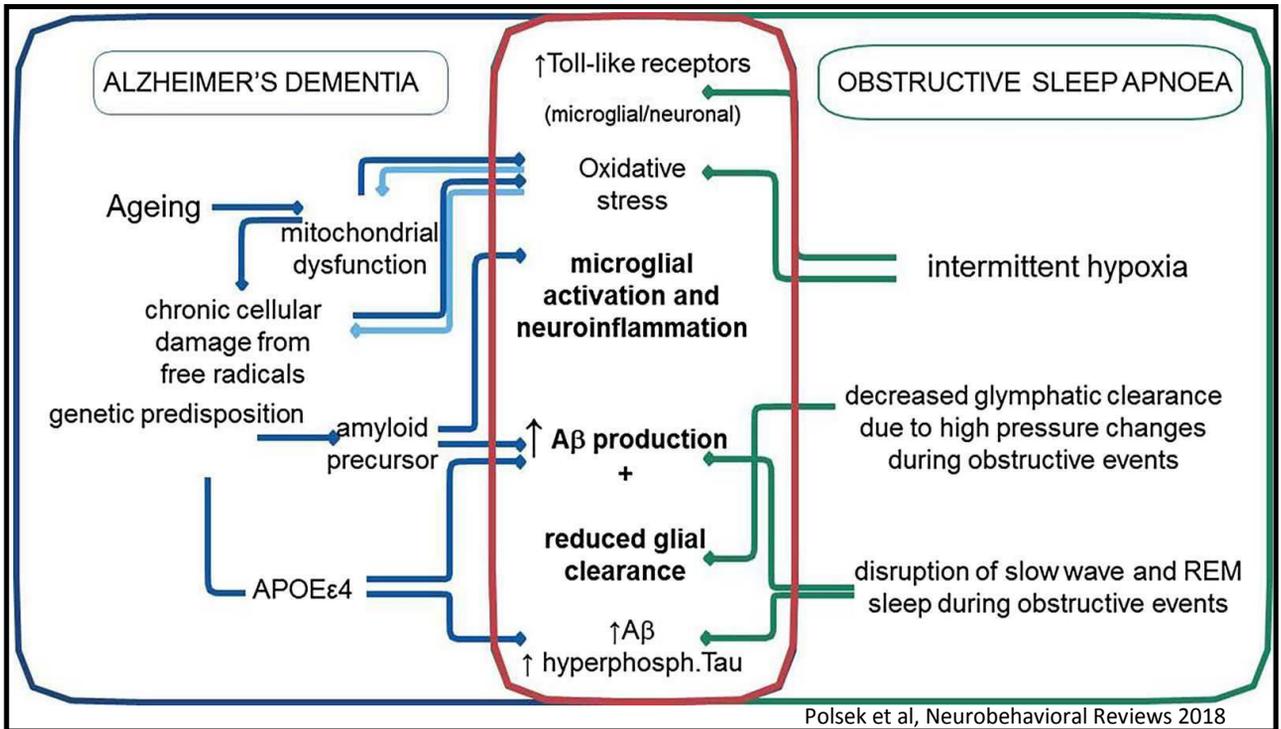
- Poor sleep quality
 - Increased sleep latency
 - Low sleep efficiency, more low amplitude SWS, less beta spindles
 - Increased wake after sleep onset, increased fragmentation
 - Increased napping
 - delay in circadian phase - causing sundowning, agitation, confusion
- ↓
- Prevalence and severity of sleep increase with dementia severity and precede dementia

Co-morbidities

- Vascular dementia: OSA (increased risk of cognitive decline)
- Demented patients have a 5 fold higher risk for OSA (Emamian et al., Front Aging Neurosci 2016)
- RLS and PLM (Brzecka A et al., Frontiers Neurosci 2018)
- DLB: RBD
- PD dementia: RLS (more arousals)
- Depression

OSA and dementia

- Common pathophysiology:
 - Reduced SWS and spindle activity in NREM
 - More sleep fragmentation
 - higher t-tau/A β 42 ratio compared to controls (Ju et al., Ann Neurol. 2016)
 - Reduced REM sleep
 - Inflammation
 - Disturbed homeostatic drive



RBD and DLB

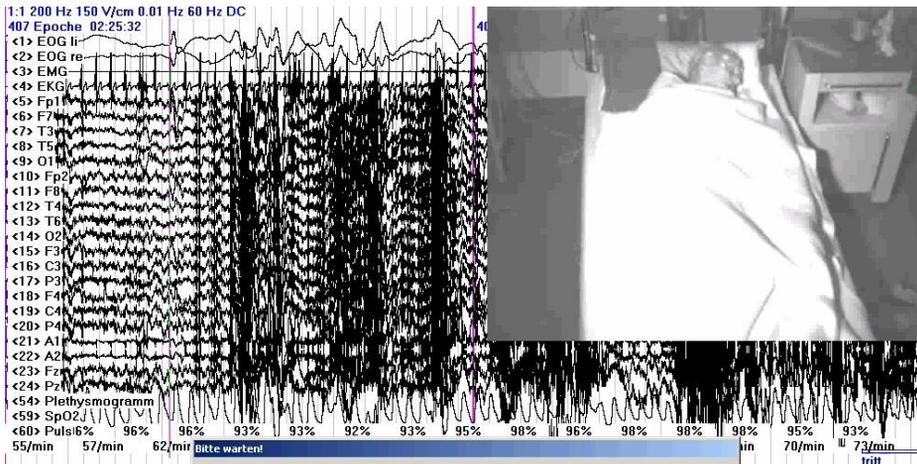
- RBD is a precursor of DLB
- Conversion
- Reduction of theta and delta power in RBD with MCI
- Reduction of alpha synuclein
- Hallucinations

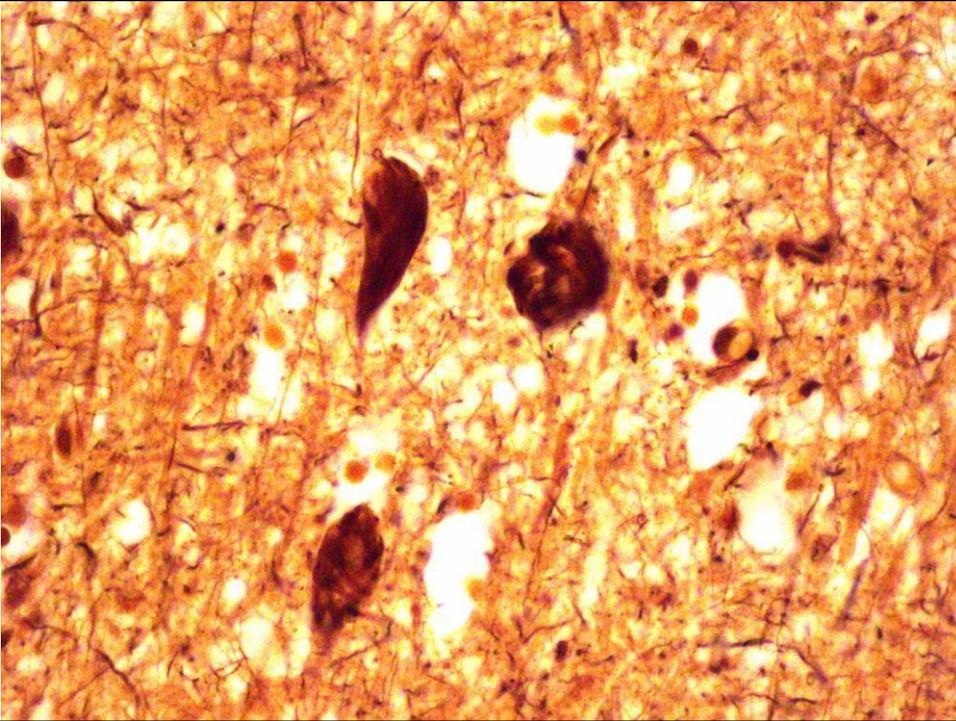
RBD

- Enactment of action filled, violent dreams: Being attacked, trying to escape threatening situations
- Vocalisations: frequently loud, emotionally packed and profane.
- Motor activity disturbs bedpartner and may be potentially dangerous for the patient and bedpartner
- Severity depends on consequences of motor behavior
- EMG: excess of muscle tone



RBD

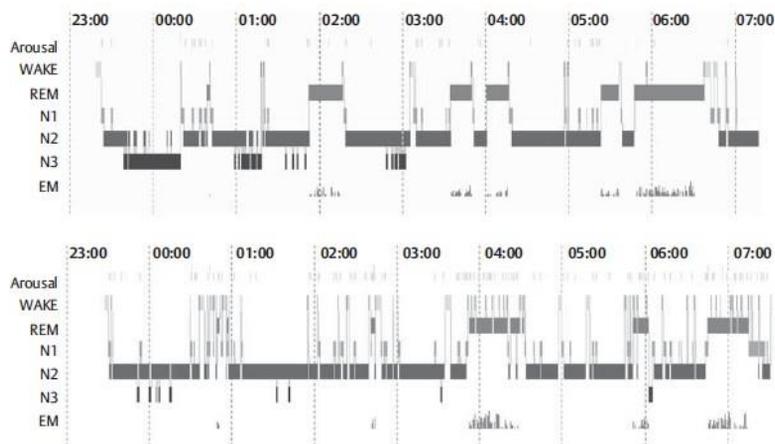




Insomnia has increased REM arousal

Riemann et al. Pharmacopsychiatry 2012

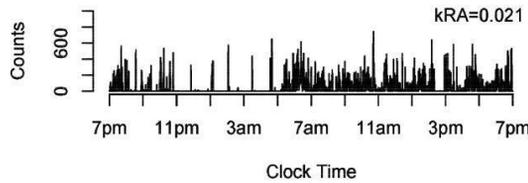
Polysomnographic profile of a good sleeper (upper panel)
and a patient with primary insomnia (lower panel)



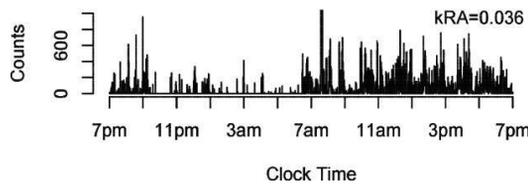
Sleep fragmentation in AD

Lim et al., Sleep 2013

A

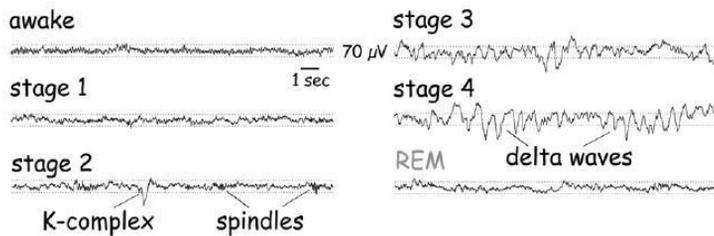
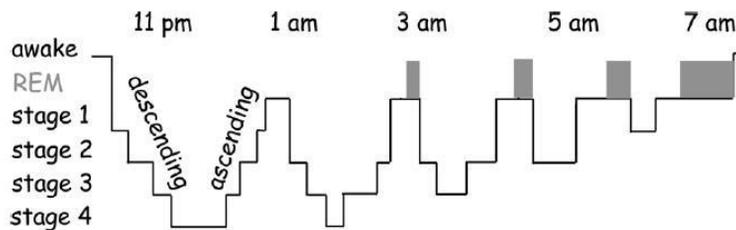


B



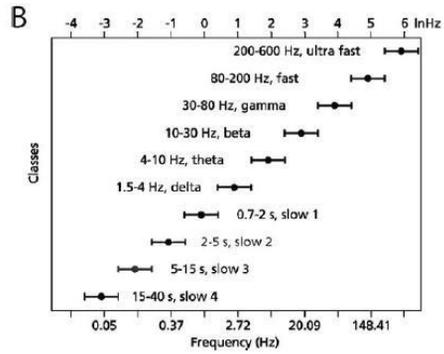
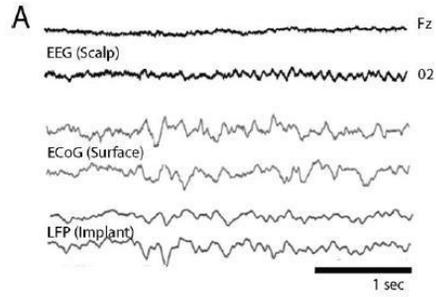
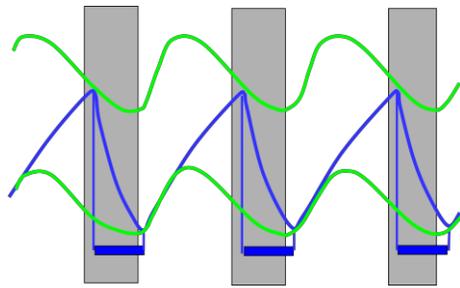
What we can see with polysomnography

Watson and Buzsáki, pms 2015



What we cannot see

Watson and Buzsáki, pms 2015

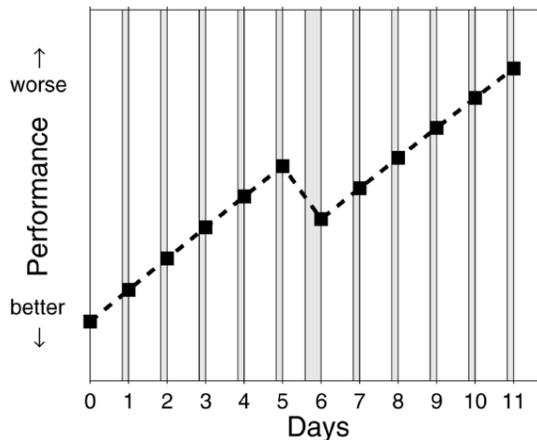


Performance restored by recovery sleep

A new mathematical model for the homeostatic effects of sleep loss on neurobehavioral performance

Peter McCauley, Leonid V. Kalachev, Amber D. Smith, Gregory Belenky, David F. Dinges, Hans P.A. Van Dongen
J Theor Biol 2009

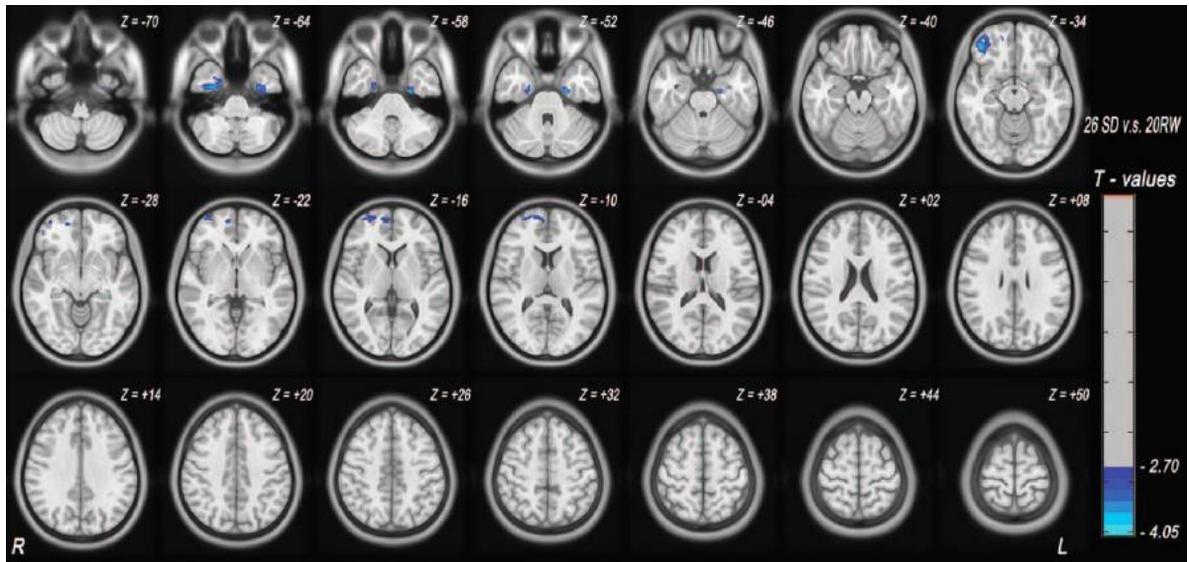
5 days 20h
wake/4 TIB
↓
1 day 14h
wake/10 TIB



ICCN Berlin 2014

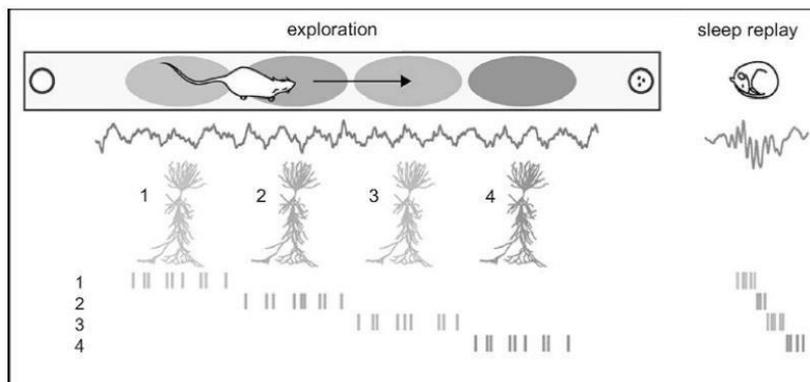
Decreased regional blood flow after 36 h sleep deprivation

Zhou et al., Medicine 98, 2019



Sleep and memory

Watson and Buzsáki, Replay of waking neuronal activity during sleep, pms 2015

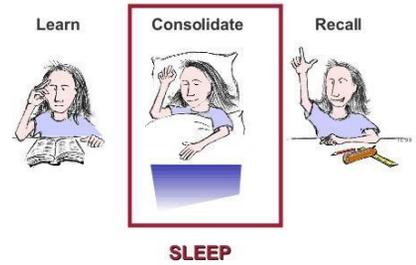
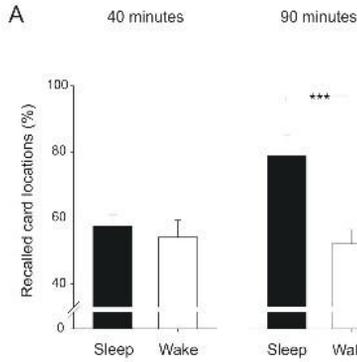


deklaratives Gedächtnis: 1. **semantic memory** (knowledge and general facts about the world) 2. **episodic memory** (events and facts from personal life) 3. **procedural memory:** automatic abilities (riding a bike, swimming)

Sleep and memory



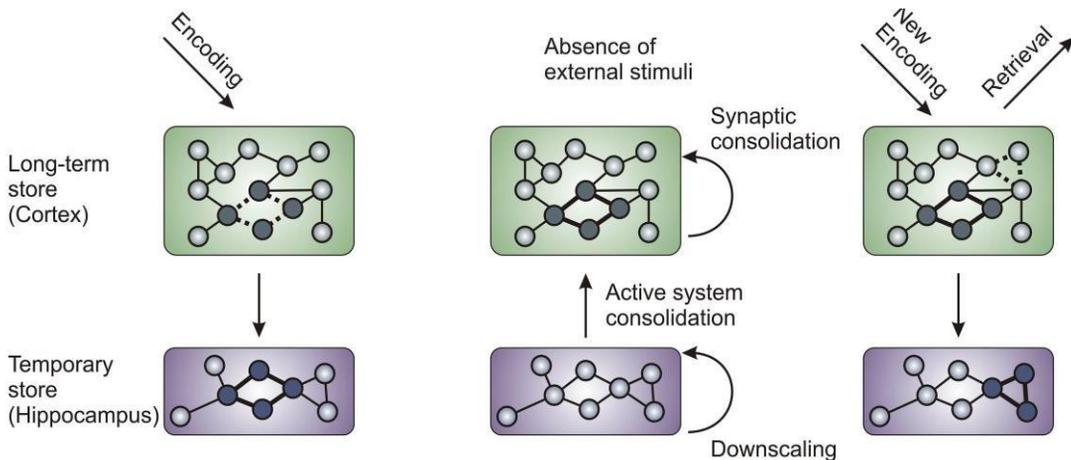
The time course of memory consolidation during sleep



Diekelmann, Biggel, Rasch & Born 2012, Neurobiol Learn Mem

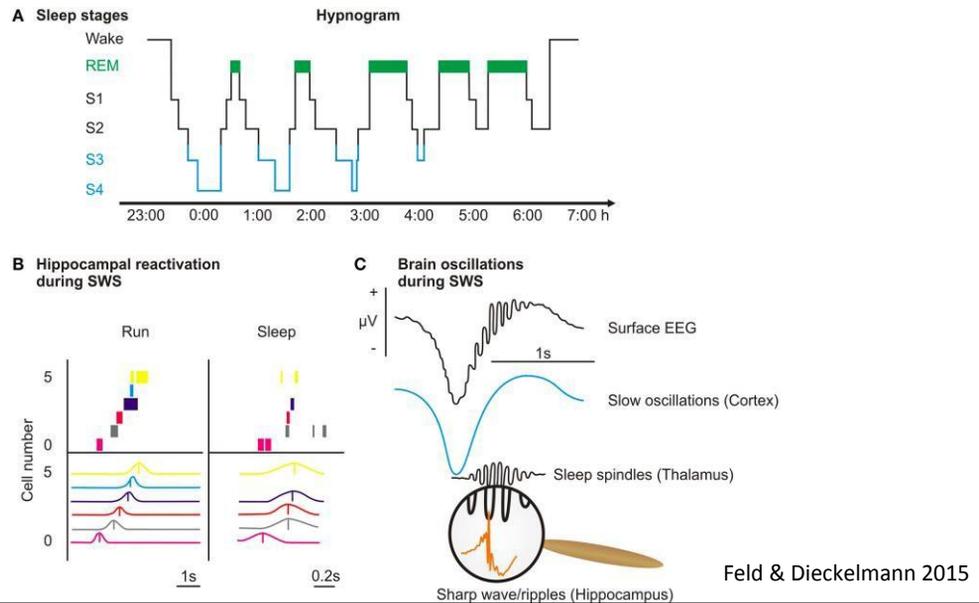
How and where does encoding take place?

Feld & Diekelmann, Frontiers in Psychology 2015



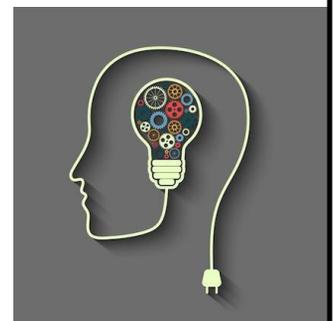
Consolidation in cortex during slow wave sleep, downscaling in REM sleep

What does the transition hippocampus to cortex look like?

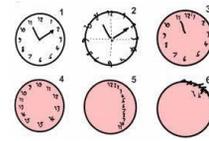


Practical consequences

- Memory consolidation occurs after 3 h of sleep, but:
 - After a complete night of sleep consolidation is much better!!
 - Sleep stages are responsible
 - Deep sleep: declarative memory
 - REM sleep: procedural + emotional memory
 - Consolidation happens after 60-90 min daytime sleep
- Sleep deprivation causes worsening of encoding
- Age = less deep sleep = slower learning



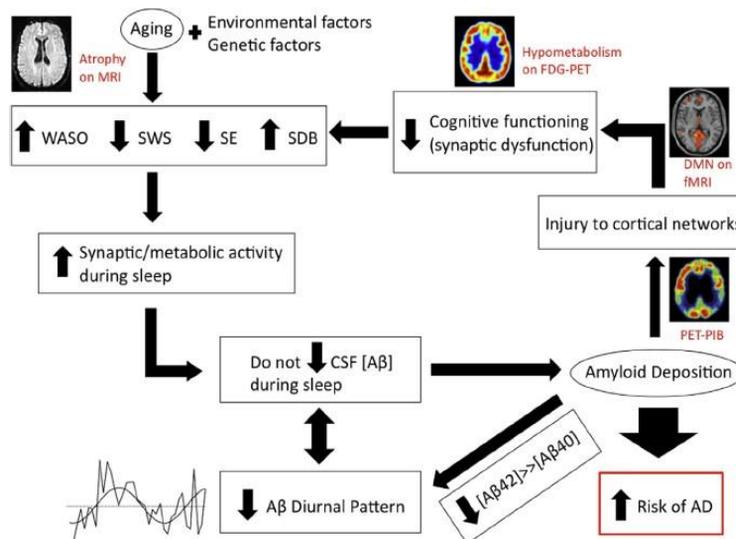
Sleep disorders and dementia



- Metaanalysis by Shi et al., Sleep Med Rev 2017 und Almondes et al., J Psych Res 2016:
 - Subjects with sleep disorders have a higher risk for dementia than those without
 - OSA is associated with the development of vascular dementia
 - Insomnia deteriorates with progressing dementia
 - Insomnia is a predictor for AD



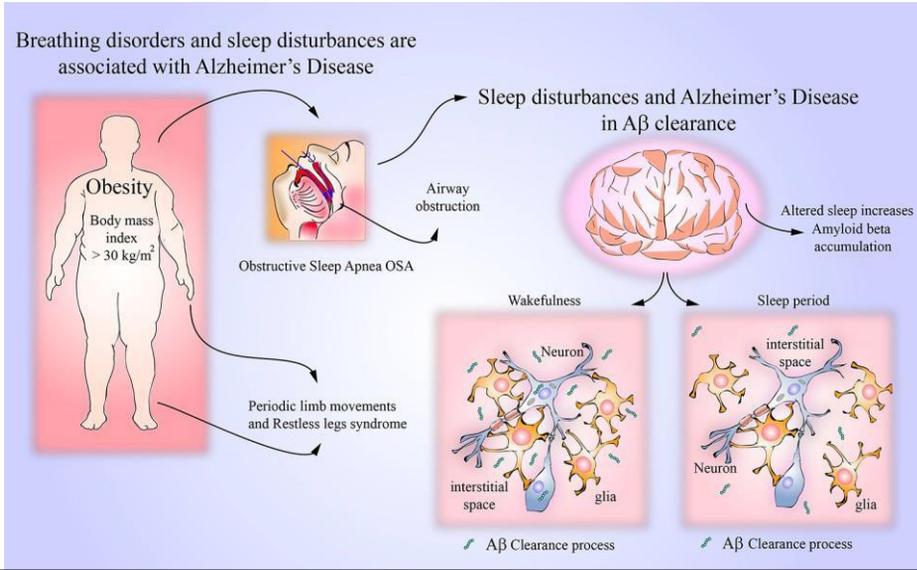
Sleep disorders and AD – a model



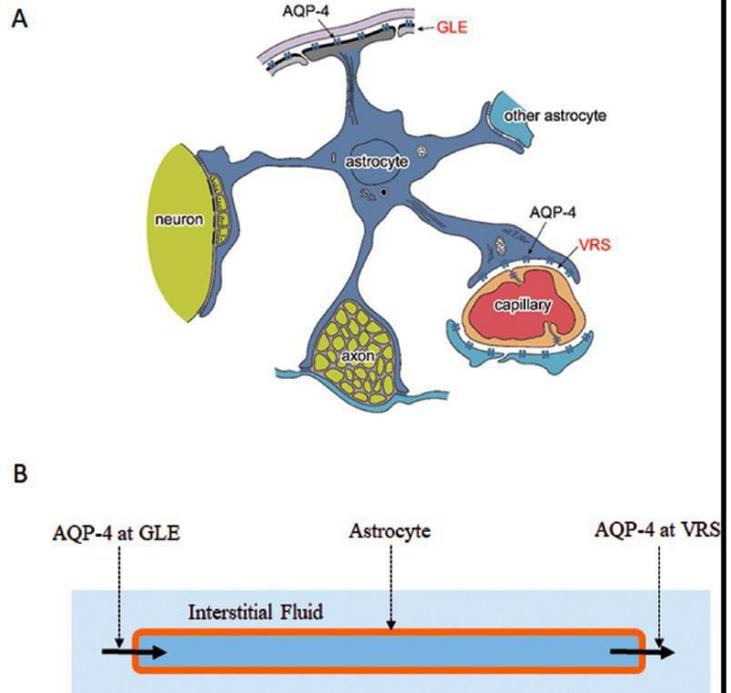
Lucy et al. 2015

Confounders and glymphatic system

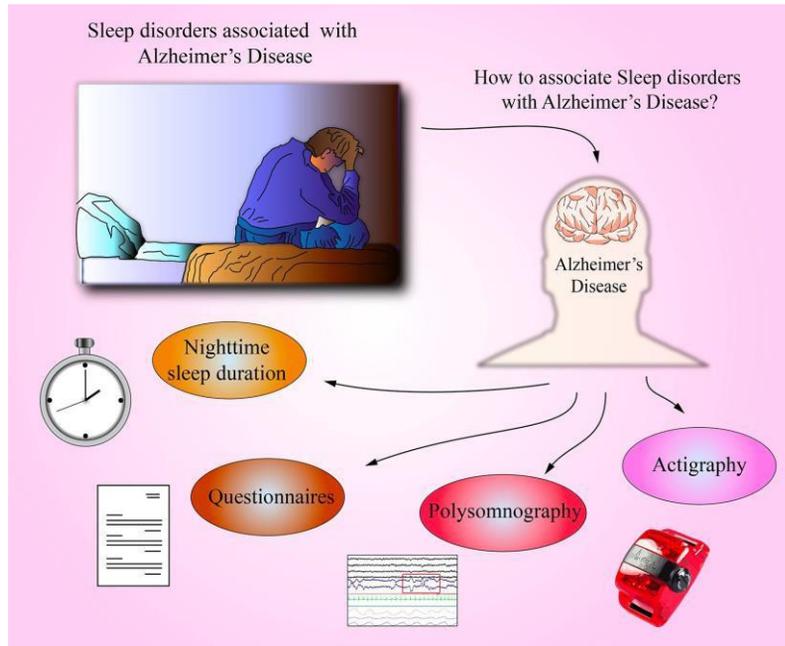
Glymphatic function, including A β clearance, is dependent upon the expression of the astroglial water channel aquaporin-4 (AQP4) that is localized primarily to perivascular astrocytic endfeet ensheathing the cerebral vasculature



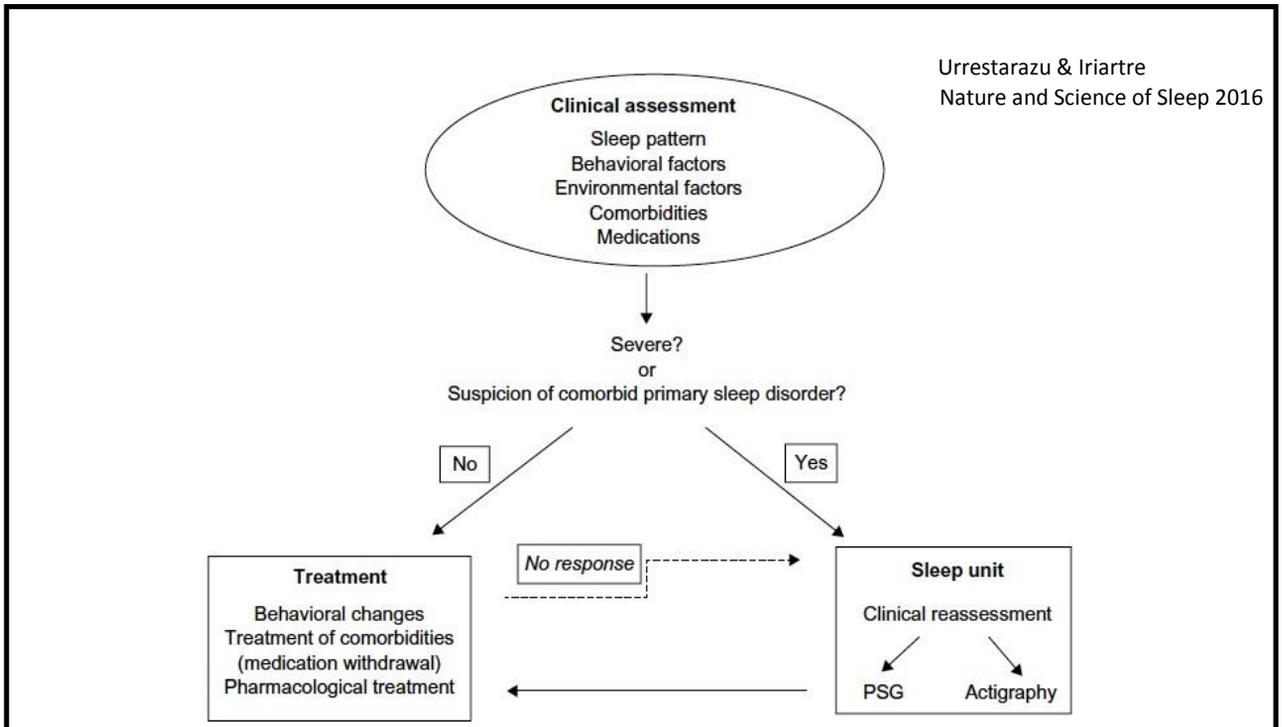
Aquaporin-4



Diagnostics



Diagnostics



Therapies

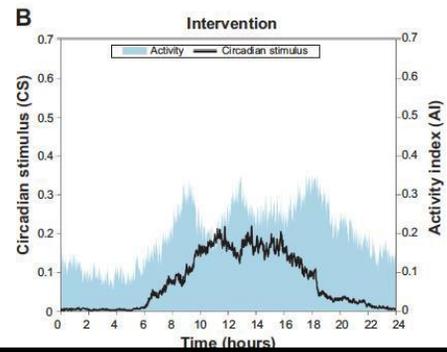
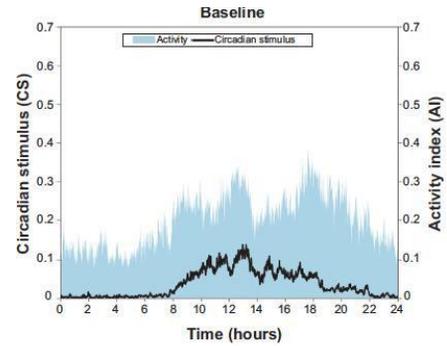
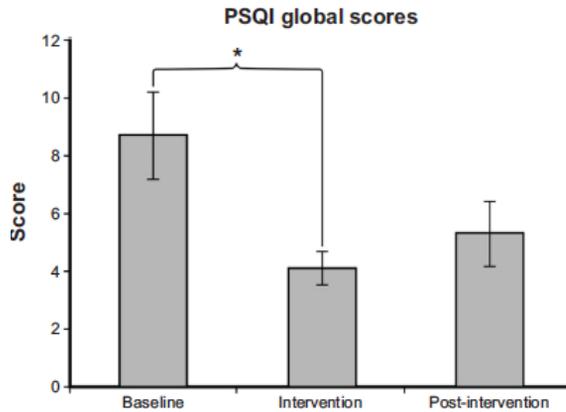
Treatment of the sleep disorders

Treatment of the sleep disorders			Treatment for AD	
Nonpharmacological	Pharmacological	Others	Improve sleep	Aggravate sleep
Behavioral measures	Melatonin ^a	CPAP	Galantamine	Donepezil
Stimulus control	Z-hypnotics		Donepezil	Rivastigmine
BLT ^b	Sedating antidepressant (trazodone ^c)		Rivastigmine	
	Antipsychotics			
	Melatonin receptor agonists ^c			
	Hypocretin receptor antagonist ^c			
	Circadian clock modification ^c			

- Melatonin alone:
 - Improved sleep onset latency and TST
 - Improves cognitive and emotional performance and daily sleep wake cycles
 - side effects: aggravation of depressed mood and withdrawn behavior
- In combination with bright light 2500 Lux reduction of side effects of melatonin (Dowling et al. 2008)

Light intervention in seniors improves sleep and agitation

Figuro 2014, Clin Interventions in Ageing



Conclusion

- Dementia and sleep are highly related
- Life style and comorbid sleep disorders may aggravate conversion to dementia by enforcement of sleep fragmentation, inflammation etc.
- The glymphatic system is impaired by sleep disturbance

Watch out for:

Sleep disorders as early signs of dementia

Treat underlying disorders early to prevent dementia

