U3A Ōpāwaho – 10 March 2026

The Importance & Mysteries of Sleep

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The Importance & Mysteries of Sleep

I. Basics on sleep
II. Why do we need sleep?
III. Microsleeps
IV. Sleep disorders
V. Sleep apnoea – and why it's bad for the brain
VI. Take home messages …

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I. Basics on sleep

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All animals need sleep

- All animals sleep – even if only ½ of brain asleep at a time (e.g., dolphins, migratory birds)
- We spend ¼ to ⅓ of our lives sleeping
  - better things to do with our time?
  - leaves animals vulnerable
- So, clearly, sleep fulfills:
  - a fundamental need of the brain – but not the rest of body
  - An essential function which evolution wasn't able to cover without sleep
- But *what* is this need? … *Later*

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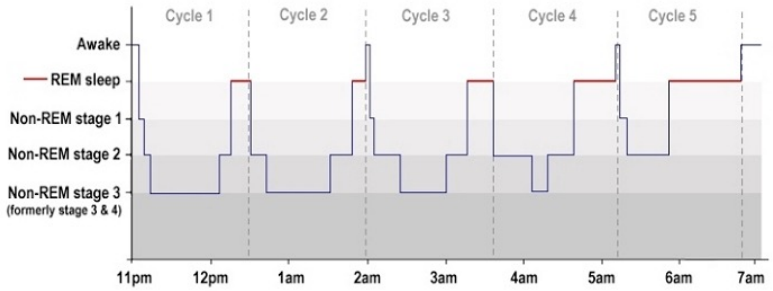
Basics

- Stages
  - Non-REM sleep
    - Stage 1 – Wake-Sleep transition
    - Stage 2 – Light sleep
    - Stage 3 – Deep sleep (= slow-wave sleep)
  - REM sleep
- Cycles ~90 min ➔ Hypnogram:



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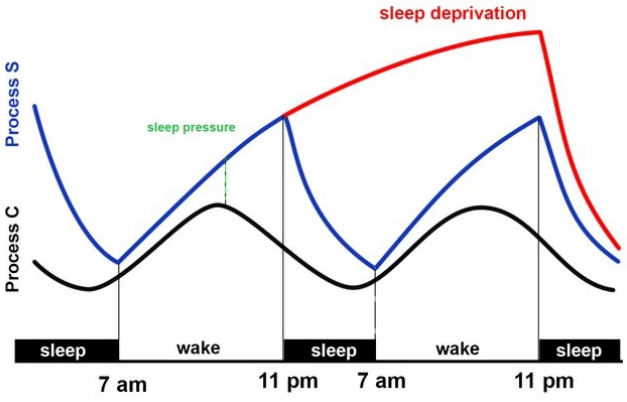
Regulation of sleep: The two-process model

- Process S – Homeostatic pressure to sleep
- Process C – Circadian arousal rhythm ➔ Partially counteracts S



- Overall pressure greatest at 2–4am and 1–3pm

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Amount of sleep

- Average = 6.8 h; Long sleepers = 9 h; Short sleepers = 5 h; Ultra-short sleepers = 3 h
- Sleep = Core + Optional
  - Most people can adapt to 4.5–5.0 h of core sleep
  - Some can get this down to ~3 h without reduced performance
- Longest study on sleep deprivation
  - In 1964, Randy Gardner (17y old) awake for 11 days.
  - Mostly recovered in a long sleep of ~14 h
- Health deteriorates if:
  - sleep < 4 hours ➔ increased risk of AD
  - sleep > 9 hours ➔ increased risk of stroke and cardiac events

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REM sleep

- REM sleep seems involved in:
  - Consolidation of memories (short-term ➔ long-term)
  - Emotional processing (particularly associated with fear)
  - Cognitive Function (mental concentration, mood regulation)

BUT little actual evidence

- Most dreaming occurs during REM - but also occurs during SWS

Brain's control of sleep

- A complex system of neuronal centres (especially hypothalamus & brainstem), pathways, and neurotransmitters for control of wake and sleep

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II. *Why* do we need sleep?

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Functions during sleep – The 3 big ones

1 ➡ Synaptic homeostasis

- Sleep's primary goal is the homeostatic regulation of the total synaptic weight impinging on neurons
- **During wakefulness** – Learning processes result in a net increase in synaptic strength in many brain circuits
- **During sleep** (primarily Stage 3) – Downscale synaptic strength to a baseline level beneficial for learning and memory
- **"*Sleep is the price we have to pay for plasticity*" (Tononi)**

2 ➡ Memory consolidation + forgetting

3 ➡ Clearance of extracellular metabolites

- Build-up during wakefulness
- Includes toxic protein aggregates

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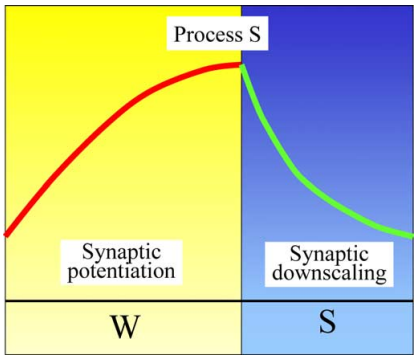
Synaptic homeostasis

- Sleep drive/propensity driven by
  1. Homeostatic component (increases during wakefulness, decreases during sleep) – Process S ➔ **Synaptic homeostasis**
  2. Circadian component (arousal propensity during 24 h) – Process C

Total synaptic strength in the brain

100 trillion synapses in human brain



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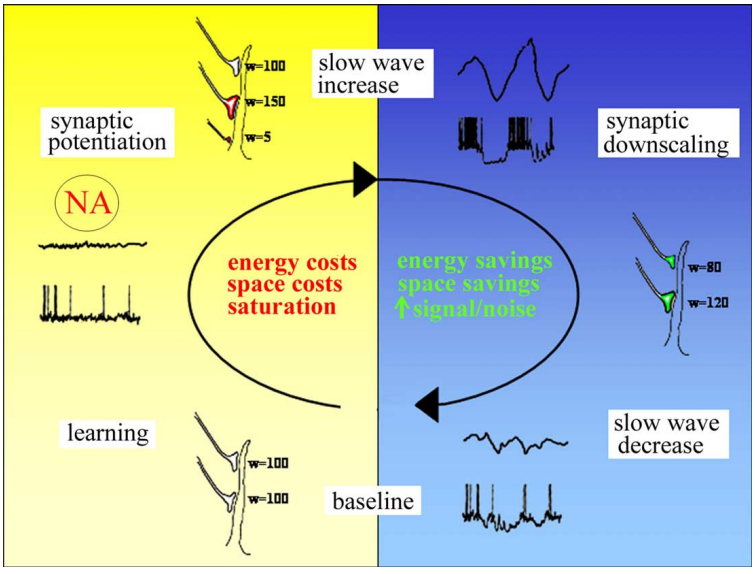
Synaptic homeostasis



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Sleep all explained? ... Far from it

Major mysteries remain:

- Why cycles of sleep states?
- Role of Stage 2 sleep?
  - Spindles? K-complexes?
- Role of REM sleep?
- Role of dreaming?
- Can one have local sleeps when awake? ➔ *Yes*
  - Could these cause attention lapses and/or errors in performance?
- And what about local wakes when asleep? ➔ *Yes - Lucid dreaming*

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III. Microsleeps

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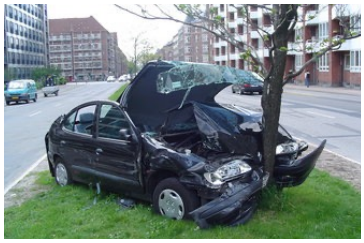
Microsleeps *versus* Drowsiness/Fatigue

- **Microsleeps**
  - Short, but complete, shutdowns in responsiveness
  - Can happen when NOT drowsy!
  - ***Extremely dangerous***
- **Drowsiness/Fatigue**
  - Feeling tired/sleepy
  - But can still do your job while drowsy
  - ***Mildly dangerous***



In-Confidence

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fMRI + EEG + Tracking + EyeVideo

In-Confidence

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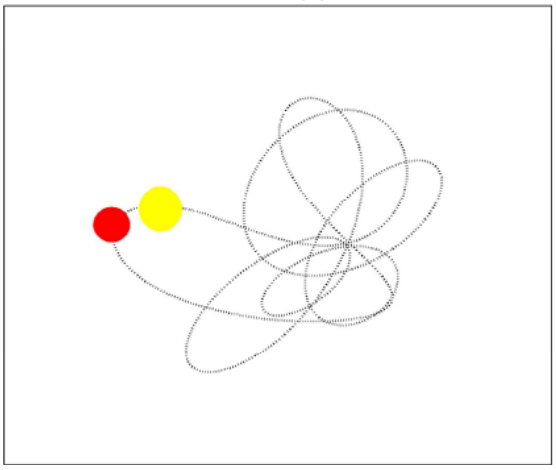
Continuous visuomotor tracking task (50 min)

- Participants performed a 2-D random tracking task



In-Confidence

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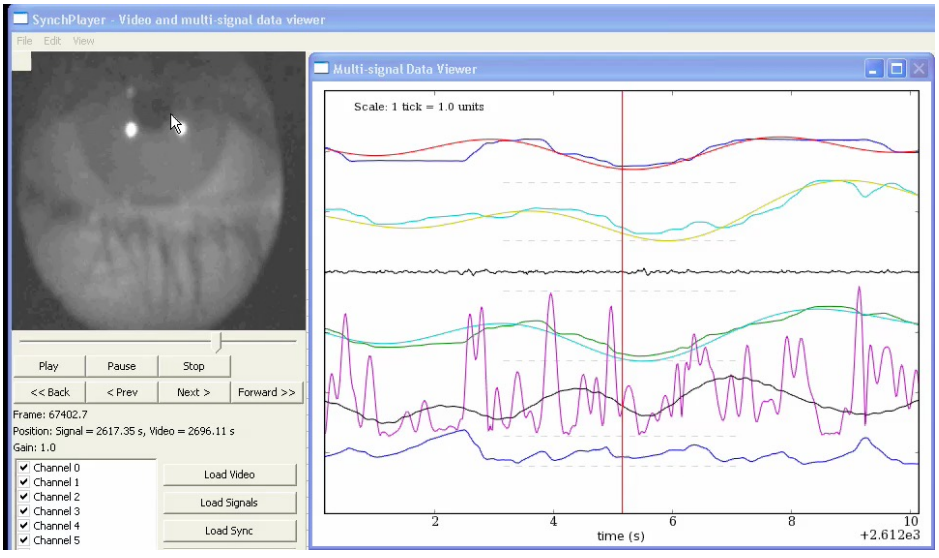
1x microsleep (5 s) in MR scanner



In-Confidence

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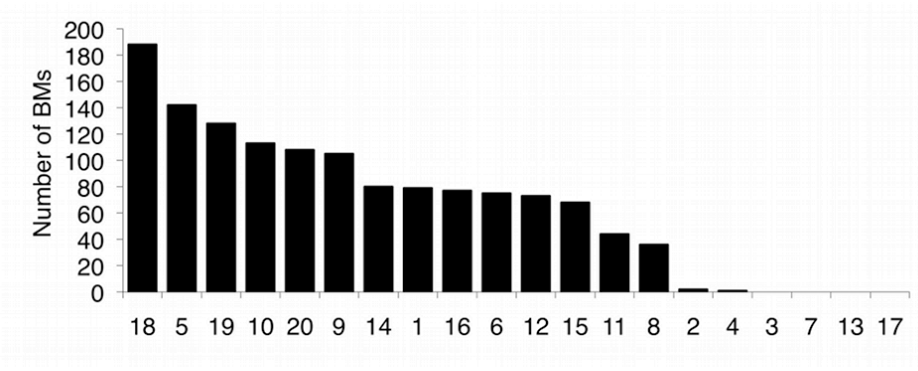
Behavioural results - *Microsleeps*

- 16 of 20 subjects had microsleeps
- Rates = 79 /h (0–225 /h)
- Durations = 3.3 s (0.5–15 s)



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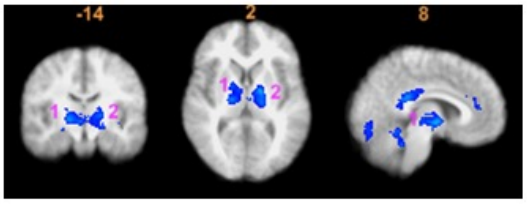
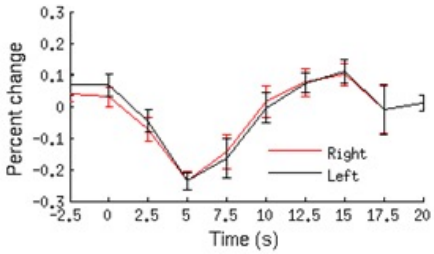
fMRI results

Decreased activity during behavioural microsleeps





Thalamus

Right = 14, -12, 2 (1)

Left = -12, -16, 2 (2)

(Poudel, …, Jones. *Hum Brain Mapp*, 2014)

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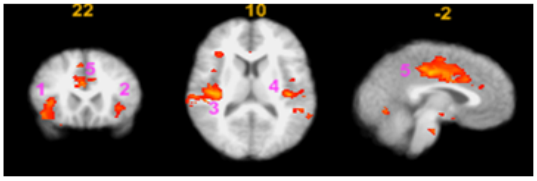
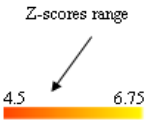
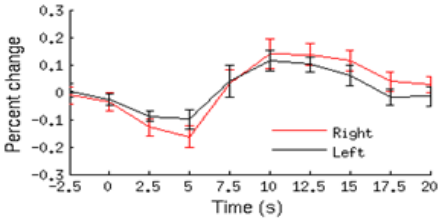
fMRI results

Increased activity during behavioural microsleeps







Cingulate gyrus

Right = 6, 18, 30 (5)

Left = -4, 22, 40 (5)

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Take-home messages: *Microsleeps*

- Most of us have microsleeps.
- Propensity varies greatly in healthy subjects.
- Can occur when not sleep-deprived.
- Propensity increases with excessive sleepiness:
  - Sleep deprivation
  - Poor/fragmented sleep (e.g., due to OSA)
  - High on sleepiness trait (Epworth Sleepiness scale).
- Big killer on the road:
  - ~20% of fatal accidents on the road (more than alcohol & drugs)
- Countermeasures:
  - A good night's sleep
  - Stimulant: Caffeine, Modafinil, amphetamine, methylphenidate, …
  - Nap (30 min)
  - Strong coffee + nap
  - Minimal eating shortly before or during long drives [RJ]
  - *Awareness*

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IV. Sleep Disorders

Adults in NZ with a chronic sleep problem

- Insomnia [27%]
- Excessive daytime sleepiness [15%]
- Obstructive sleep apnoea
  - [12%: World-wide – Moderate = 500 million; Severe = 300 million (*Lancet Respir Med* 2019); Mild-severe = 1 billion]
- Restless leg syndrome [4–14%]
- Parasomnias [3%]
- REM sleep disorder [0.4–0.5%]
- Narcolepsy [0.04%]

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V. Sleep apnoea – And why it's bad for the brain

1. **Impaired cerebral perfusion**
2. **Links to Alzheimer's and Parkinson's disease**

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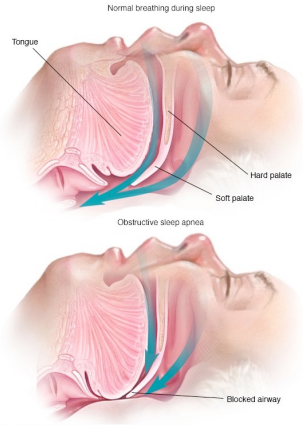
What is obstructive sleep apnoea (OSA)?

- In OSA, muscles in the upper part of the throat, which normally keep the airway open, relax during sleep and cause the airway to become
  - fully blocked for 10-60 s ➔ apnoea
  - partially blocked for 10-60 s ➔ hypopnoea
- Respiratory disturbance during sleep due to OSA leads to
  - cyclical oxygen desaturation in the brain
  - frequent arousals
  - sleep fragmentation



- Severity of OSA
  - AHI index = Number of apnoea/hypopnoeas per hour
  - Mild = 5–14 Moderate = 15–29 Severe ≥ 30

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Obstructive sleep apnoea

Untreated OSA is associated with –

- Hypertension
- Cardiovascular disease
- Stroke
- Diabetes
- Decreased cerebral perfusion
- Cognitive dysfunction
- Excessive daytime sleepiness
  - ➔ Increased risk of *microsleeps*
  - ➔ Increased risk of fatal accident on the road

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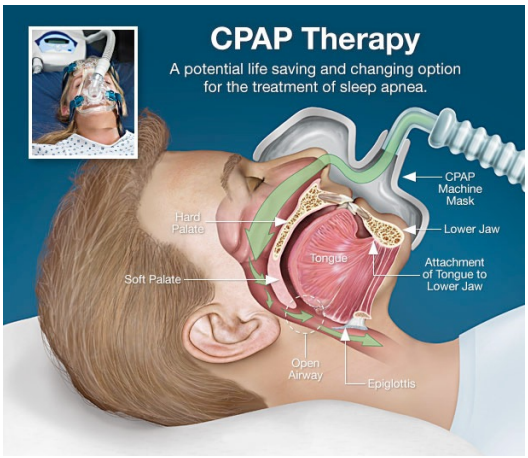
Treatment of OSA – *Continuous positive airway pressure* (CPAP)

- CPAP during sleep is the treatment of choice.



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CPAP

- In NZ, CPAP is publicly funded but only for people with severe OSA.

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Why is sleep apnoea bad for the brain?

#1 = *Impaired cerebral perfusion*

Cerebral perfusion – Amount of arterial blood delivered to each voxel in brain

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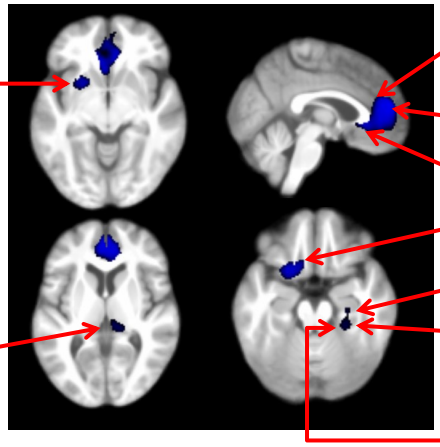
Study 1 – Regional Perfusion: Moderate-Severe OSA *versus* No OSA



[Innes, … , Jones. *Sleep*, 2015]

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Study 2 – Cerebral perfusion in ***moderate***-OSA?

Reduced function and brain damage?

- Several studies have shown impaired cerebral perfusion in severe-OSA when awake
- BUT what about less severe OSA?

Research Study 2 (longitudinal)

- Effects of moderate-OSA when asleep on brain function when awake on:
  - Cerebral perfusion
  - Cognition
  - Microsleep propensity
- Benefit of 6 months of CPAP treatment.

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Method

Subjects

- 26x referrals to Sleep Unit (symptomatic) with confirmed moderate-OSA (AHI = 15–30)
  - 13x ➔ CPAP treatment for 6 months
  - 13x ➔ No treatment
- 7x healthy controls (AHI ≤ 5) ➔ No treatment

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Results – Cerebral Perfusion at Baseline

Between moderate-OSA and control:

- No significant difference

➔ **Cerebral perfusion *not* significantly impaired in moderate-OSA**

➔ **Blood-flow regulatory mechanisms in the brain can cope with the adverse effects which occur in moderate – *but not severe* – OSA**

[Buckley, … , Jones. *Sleep & Breathing,* 2024]

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Overall – Moderate-OSA versus Controls

At baseline

- Cerebral perfusion ➔ Not impaired
- Cognition ➔ Not impaired
- Microsleep propensity ➔ Not impaired

At 6 months

- No difference between CPAP and non-CPAP groups

➔ ***No evidence of impairment of brain function in moderate-OSA***

➔ ***So, no benefit of CPAP in moderate-OSA ?***

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Excessive daytime sleepiness?

CPAP-treated group

Desire to continue CPAP

- 12 of 13 CPAP-treated patients considered they had benefitted from CPAP to extent that they wished to continue CPAP following the study.

Reduction in daytime sleepiness – *Epworth sleepiness score*

- Baseline ESS:
  Mod-OSA = **13.0** vs. Controls = 7.0 ($p < 0.001$)
- Improvement in ESS at 6 months:
  Mod-OSA = **8.0** ($p = .004$)

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Why is sleep apnoea bad for your brain?

#2 = *Links to Alzheimer's disease and Parkinson's disease*

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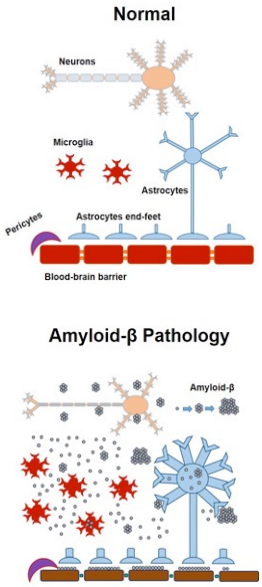
Alzheimer's disease

- Aggregates of toxic protein metabolites in the brain —amyloid-β plaques and phosphorylated-tau tangles — are the hallmark of Alzheimer's disease.
- Abnormal accumulation of these metabolites results from an imbalance between their production and clearance.
- Various clearance systems transport Aβ across the blood–brain barrier – particularly the *glymphatic system*.



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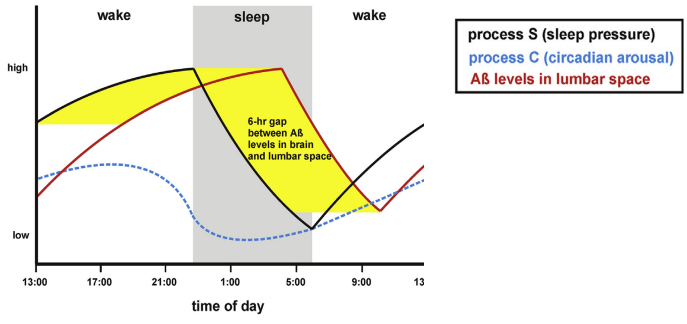
Sleep and clearance of amyloid-β [Cedernaes et al. *Sleep Med Rev* 2016]

- During wakefulness, extracellular levels of these toxic metabolites in the brain increase.
- Sleep facilitates removal of these metabolites.



➔ Insufficient or disrupted sleep (as in OSA)
➔ reduced clearance ➔ abnormal levels of amyloid-β

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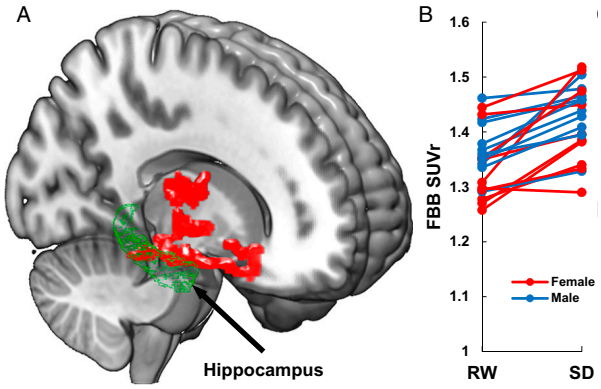
Amyloid-β accumulation after 1 night of sleep deprivation

[Shokri-Kojori et al. *PNAS* 2018]

- 20 healthy subjects (10M:10F, 22–72 y) completed two PET scan sessions (18F-florbetaben) to measure Aβ: Rested vs. 1-night SD (31 h).
- Significant increase in Aβ burden in R-hippocampus and R-thalamus.



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But could increased amyloid in OSA be due to something other than poor sleep? ➔ *Yes* – Hypoxia

- **Animal study (mice)**:
  - Repeated hypoxia ➔ increased level of amyloid-β
    [Shiota et al. *J Alzheimer's Dis* 2013]
- OSA is characterized by nocturnal intermittent hypoxia.

➔ Chronic intermittent hypoxia – as occurs in OSA – contributes to the pathogenesis and onset/progression of Alzheimer's disease.

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OSA and Alzheimer's disease – Summary

- Sleep apnoea increases
  - *Risk* of developing AD
  - *Rate* of progression of AD
- Mechanism – Reduced clearance of amyloid-β and P-tau due to:
  - Poor/fragmented sleep
  - Chronic intermittent hypoxia

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Link between OSA and Parkinson's disease

Impaired clearance of α-synuclein

- Pathological hallmark of PD = presence of misfolded α-synuclein protein in the form of Lewy Bodies [Irwin & Hurtig, 2018; Sun et al., 2019].
- Prevalence of sleep disorders in PD is 40–90% [Chou et al., 2017].
- Levels of α-synuclein [Sun et al., 2019] -
  - higher in patients with OSA than controls
  - positively correlated with severity of OSA

  ➔ Poor sleep + chronic intermittent hypoxia ➔ increased levels of α-synuclein

  ➔ Pathogenesis of PD
- Patients with OSA at 2x risk of PD [Chen et al., 2015].

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Treatment of Parkinson's disease

Currently, no medication slows the underlying pathology in PD

How about CPAP?

- Study investigated CPAP in the treatment of motor function in PD patients who also had OSA [Meng et al. *Parkinsonism Relat Disord* 2020]
- Following 12 months of CPAP:
  - ➔ **Smaller *decreases* in motor function** in OSA+CPAP than in:
  - – OSA but no CPAP
  - – and even ***no OSA***
- Do the benefits of CPAP in PD also apply to
  - – cognitive decline?
  - – PD without OSA?

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VI. Take-home messages

Obstructive sleep apnoea

- Untreated OSA (especially if severe) associated with –
  - cardiovascular disease, stroke, diabetes, reduced cerebral perfusion, cognitive dysfunction
  - Increased risk and rate of progression of neurodegenerative disorders
    - Alzheimer's disease
    - Parkinson's disease
- CPAP is treatment of choice.
- If you (or your partner) are concerned about possible/definite OSA, see your GP re possible referral to a Sleep Unit.

Insufficient sleep - Sleep disorder or sleep deprivation

- Excessive daytime sleepiness
  ➔ *Increased propensity for microsleeps* ➔ *risk of fatal accident*

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