Sleep and Dementia

Elissaios Karageorgiou, MD PhD
Memory and Aging Center
University of California San Francisco

October 3rd, 2015

Talk outline

- Why (and how) we sleep
- Sleep and aging
- Relationship between sleep and dementia
- What should we be doing with what we know?

Conflict of interest

Do we really need to sleep?

I've always loathed the necessity of sleep. Like death, it puts even the most powerful men on their backs. - Frank Underwood

"I ain't showin' nothin', and I ain't tellin' nothin'"
Why we sleep…

- Ecological Homeostasis
- Dynamic Brain Organization
- Energy conservation
- Tissue restoration
- Synaptic preservation & plasticity
- Survival advantage
- Memory consolidation
- Immune modulation
- Brain development


The sleep-wake cycle: Circadian rhythm and Homeostasis

- Adenosine buildup from ATP breakdown
- Circadian regulation
- Body temperature and melatonin over 24 hours

Day 1
Day 2


Circadian regulation

- Pathway of melatonin production
- Arousal network
- Sleep promoting network

Sleep architecture

- Normal sleep is divided in cycles – 4-5 per night
- Each cycle goes through stages
- Each stage depends on brain waves as picked up by the EEG (electroencephalogram)
- Faster REM (Rapid eye movement) sleep
  - Later in sleep
  - Vivid dreaming
- Slower Non-REM sleep (N1, N2, N3)
  - Deep / Slow wave sleep (SWS) early in sleep
  - Restful sleep
- Memory consolidation during sleep
  REM: procedural and emotional
  NREM: episodic

Sleep cycle characteristics

Circadian cycle and architecture changes with aging

- Melatonin secretion and body temperature drop occur earlier in the night (urge to sleep earlier)
- SWS decreases (less rested sleep)
- Outcome:
  - People push themselves to sleep later to be socially active
  - Nighttime awakening when temperature starts to increase again
  - More daytime naps and dozing off
Sleep pattern changes with “aging”

- **Daytime napping**
  - Increased association to all cause mortality by 14-32%.
  - However, napping could also be helpful, especially if addressing recent sleep deprivation (e.g. partying all night).

- **Circadian (sleep-wake) rhythm breakdown**
  - Not having well consolidated sleep and separate from daytime wakefulness.
  - 22% faster annual cognitive decline and risk for AD increased by 20-50%.

- **Insomnia**
  - >9h worse than <6h.
  - Conflicting evidence.

Sleep disordered breathing (SDB) and aging

- **Study of Osteoporotic Fractures in Women**
  - 298 women (~80 yo), 105 SDB (35%) vs. 193 non SDB (65%).
  - Target outcome: Development of MCI or dementia.
  - 45% advanced of those with SDB vs. 31% of the women without SDB.
  - Likely mechanism: hypoxia (less oxygen reaching the brain). Also verified by recent pathology studies.

- **Study of Osteoporotic Fractures in Men**
  - 2,636 men (~75 yo).
  - Up to double the decline in global cognitive performance compared to unaffected, or less affected, men.
  - Again hypoxia linked as the most likely mechanism.

- **Big Picture**
  - SDB is present in 50% of demented vs. only 5% of non-demented individuals.
  - Hypoxia significance also for SWS where blood perfusion to the brain drops by half.
  - SDB is treatable!

Are aging and sleep disorders inevitably bound together?

- **Sleep in America Survey**
  - 1500 adults (55-85 yo).
  - If no comorbidities 10% poor sleep.
  - With >1 comorbidity up to 41% poor sleep.

- **Importance: Dissociation between poor sleep and aging**

  - “Aging alone does not cause sleep problems, but all the things that accompany aging”

  - Illness.
  - Medications.
  - Circadian rhythm disorders.
  - Primary sleep problems.

So, if sleep disorders in aging are not necessarily linked to aging... then?

- **Amyloid deposition in dementia**
  - and non-demented individuals.
  - Clinical AD diagnosis often does not reflect fibrillary amyloid pathology.
  - Healthy older controls are more likely to have amyloid pathology than younger controls.


Foley et al. J Psychosom Res. 2004; Foley et al. Sleep 1999

Ossenkoppele et al. JAMA 2015
Conceptual approach to dementia

- Neurodegenerative diseases target distinct brain networks with partial overlap
- Early degeneration often occurs at the brainstem in certain dementias
  - Alzheimer disease, synucleinopathies, progressive supranuclear palsy
- Sleep-wake centers are located in these areas and there is abnormal protein accumulation in these centers early on

Sleep changes in dementias

- Sleep disorders in “healthy” ages partially predict future dementia
  - Brainstem involvement (where sleep centers are) prior to disease reaching the cortex (where higher cognitive functions take place, such as memory)
- Degenerative dementias with overt sleep disturbances (fragmentation, insomnia, SDB) likely have early brainstem pathology
  - AD
  - Synucleinopathies (DLB/PD/MSA)
  - PSP
- Certain dementias have unique sleep patterns
  - REM behavior disorder in synucleinopathies – “living the dream”
- Conclusion: sleep disturbances in dementias are accentuations of the sleep disorders of “aging”

From pathology to sleep disruption

- Increased alertness during sleep
- Insomnia
- Lighter sleep
- Sleep fragmentation and waking after sleep onset
- Daytime somnolence
- Earlier melatonin secretion
- Advanced sleep phase
- Sundowning

A bidirectional relationship

Brain Degeneration

Sleep Disorders

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**Increased neuronal activity leads to increased amyloid deposition**

- Genetically modified mice at risk of amyloid accumulation
- Measure of interstitial Aβ before plaque deposition in several areas
  - Association to subsequent plaque formation
    - Levels of lactate (measure of neuronal activity)
    - Additional focus in barrel cortex: outcomes dependent on vibrissal stimulation/deprivation

**Sleep duration and amyloid in mice**

**Manipulation of sleep-wake duration in mice prone to develop amyloid**

- Increase sleep in mice
  - More SWS → less amyloid

- Sleep deprived mice
  - More awake → more amyloid

**Implication:** Sleep is good for avoiding amyloid deposition

**Amyloid and SWS in humans**

- Association between amyloid, SWS, overnight memory consolidation
  - 26 cognitively normal participants (~75 yo)
  - Delayed recognition performance task
  - Aβ correlates with less SWS in medial prefrontal cortex (mPFC)
  - Overnight memory consolidation impaired
- Importance:
  - First in field using amyloid biomarkers for SWS-AD
  - mPFC metabolically active in REM and memory consolidation

**So what happens to amyloid during sleep?**

- Aβ clearance relates to sleep-wake pattern
- Aβ clearance pathways:
  - Aβ accumulates in the interstitial space and its amount cycles with the sleep-wake cycle (increased clearance during sleep)
  - 40% cleared via glymphatic system (interstitial flow [CSF and perivascular])
  - 60% cleared via BBB
  - Unclear how the recently identified lymphatic system plays a role
  - Once plaques develop though the Aβ diurnal fluctuation attenuates and clearance is impaired
**From sleep disruption to pathology**

- Increased neuronal activity
- Increased amyloid deposition
- Lack of deep sleep and restoration
- Hypoxia
- Sleep disordered breathing

**Sleep Disorders**

**Brain Degeneration**

**Treatment considerations**

- Hypoxia
- Sleep disordered breathing
- Lack of deep sleep and restoration
- Increased amyloid deposition
- Increased neuronal activity

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**Sleep apnea and nocturia**

- **Hypothesis**
  - Children study
    - 28 children with and 20 without OSA
    - AHI (Apnea-hypopnea index) from 17.4 to 3.3
    - Lowest SatO2 increased from 78% to 95%
  - Adult treatment study with CPAP in 12 patients
    - AHI from 81 to 19
    - Decreased nocturnal diuresis

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**CPAP for sleep apnea in dementia**

- **Cross-over sham-controlled trial**
  - CPAP treatment in 52 AD patients with OSA
  - Average use: 5h/night
  - AHI: 29 to 5
  - Deeper sleep achieved
  - Marginal benefit on composite cognitive score

- **Meta-analysis of CPAP effects on cognition**
  - 13 studies
  - 1744 middle-aged obese participants
  - Marginal benefit on vigilance only

- **Limitations**
  - Short term follow up
  - Variable populations

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Pharmacotherapies for insomnia in dementia

- Review of RCT on AD and insomnia
  - All outcomes via actigraphy
  - Melatonin no benefit in AD
    - 209 moderate to severe AD
    - Some limitations
  - Ramelteon studies
    - 74 mild to moderate AD
    - No benefit for 8 mg dosing
  - Trazodone studies
    - 30 moderate to severe AD
    - 50 mg qHS
    - *Increased sleep by 43 min and sleep efficiency
    - *No side effects during daytime

Cholinesterase inhibitors and AD

- Cholinesterase inhibitor dosing and sleep
  - 92 mild to moderate AD patients
  - Donepezil at night vs. Galantamine in the morning
  - Worse performance on sleep quality and daytime somnolence for Donepezil group
  - Half of Donepezil group switched to daytime dosing and improved sleep quality
- Effects of ACh in SWS
  - Worse memory consolidation

What to discuss with my physician?

- Time to bed and out of bed and bathroom visits (ADH effect)
- Total sleep time (and day napping)
  - Being a “very good sleeper” (>9h) also raises a red flag
- Are you “living the dream?”
- Medications, medications, medications!
  - Most medications (and several supplements) can disrupt sleep architecture
  - Verify the appropriate time for dosing a medication
- Ask for a sleep questionnaire, keep a sleep diary, consider activity tracker

What should I pursue?

- Sleep hygiene
  - Avoid unnecessary naps, avoid stimulants after 2 pm (even coffee), pursue exercise in daytime, avoid heavy meals near bedtime, sunlight exposure, regular schedule, go to bed when sleepy (no food or TV), comfortable sleep environment, do not eat in the middle of the night
  - Morning exposure to phase advance vs. late afternoon to phase delay
- Light exposure for consolidating sleep-wake cycles – Set that clock!
  - Consider light box 10,000 lux for 30 min at least if living with Karl (i.e. foggy)
  - Morning exposure to phase advance vs. late afternoon to phase delay
- Daytime exercise and regular schedule
  - No caffeine after 2 pm, no alcohol near bedtime
    - rebound insomnia esp. red wine
- Shower 1-2 hours prior to bedtime (trick your core body temperature)
- Medications, medications, medications
  - ± Trazodone (or Melatonin)
    - AChEi morning dosing
  - Remove offending agents as able (e.g. BZD)
- Talk to a sleep physician

References:
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- Song et al. Int Clin Psychopharmacol 2013
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- El-Sayed Eg J Chest Dis and Tuberculosis 2012
Thank you!

- **Memory and Aging Center**
  - Bruce Miller, MD
  - Keith Vossel, MD MSc
  - Christine Walsh, PhD
  - Kamalini Ranasinghe, MBBS PhD
  - Alex Beagle, BA
- **VAMC – San Francisco**
  - Thomas Neylan, MD
  - Leslie Ruoff, BSc RPSGT
- **Biomagnetic Imaging Laboratory**
  - Sri Nagarajan, PhD
  - Danielle Mizuiri, BSc
- **Research support:**
  - American Brain Foundation
  - Alzheimer Association
  - Tau Consortium