Maine Sleep Society
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Sleep Disorders in the Elderly:
Implications on Cognitive Function

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Objectives

• Describe the role of sleep in memory and learning
• Discuss how sleep disorders may impact cognition in the elderly
• Review the neurocognitive consequences of untreated OSA and the association with dementia
• Link treatment of sleep disordered breathing with improved cognitive outcomes

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Sleep as We Age

Along with physical changes, our sleep patterns change as part of the normal aging process.

The challenge, as clinicians and those in the sleep field, is to understand what is normal, what is pathology, and how we can help?
The Problem

- **44%** > 65 y/o’s report sx of **insomnia** at least a few nights/week
- **6/10** healthcare professionals do not feel that they have enough time to discuss insomnia during regular office visits
- Older people often expect to have sleep disruption, so may not bring it up on their own

- Chronologic age does not reflect **physiologic** age
  - Sleep disruption often associated with medical & psychiatric co-morbidities.
  - 24% diagnosed with 4+ medical conditions & 80% of this group reports sleep problems

- Sleep disorders are more common as we age
  - Insomnia, Sleep apnea, Restless legs syndrome, & REM behavior d/o
Sleep ≠ Rest

- Sleep is an **active** physiologic and metabolic process
- Complex autonomic changes coordinating BP, HR, RR and oxygenation
- Restoration of brain function, consolidation of memories/learning, and physiologic recovery

**Vital role in maintaining health impacting cardiovascular health, longevity, mood, and thinking**

Sleep Architecture
Stages of NREM Sleep

N1

N2

N3 – Slow Wave Sleep
REM Sleep

Low voltage EEG, Paralysis of most muscles, Rapid eye movements
Normal Sleep Architecture in Young Adult
Aging leads to changes in Sleep Architecture

Increased Stage 1
Aging leads to changes in Sleep Architecture

Less Slow Wave Sleep
Aging leads to changes in Sleep Architecture

REM time reduced
Aging leads to changes in Sleep Architecture

- Sleep efficiency drops
- Frequent brief arousals (15/hr)
- Early morning waking
Aging and Sleep

• Fundamental age-dependent changes in the regulation of sleep
  – Impacts on the homeostatic regulation
    • Inability to sustain long bouts of uninterrupted sleep
    • Daytime napping is more common
  – Impact on circadian regulation
    • Tendency for advanced sleep phase (“Early Bird”)
    • Less able to phase shift (schedule is more set)

• **Misconception:** Older adults need less sleep
• **Truth:** Sleep needs remain the same through adulthood
  → Disrupted sleep leads to objective daytime sleepiness
Sleep and Cognition

Healthy Brain Aging: What Has Sleep Got To Do With It?
Malhotra and Desai
Anatomy of Memory

- **Short term memory**
  - Transient pattern of neuron communication
  - Frontal lobe (especially dorsolateral prefrontal cortex) & the parietal lobe
Anatomy of Memory

• Long term memory
  – Stable, permanent changes in neuron connections
  – Widely spread throughout the brain
  – Some areas thought to be essential for specific types of memory
    • E.g. Amygdala = emotional memory
Sleep and Memory Formation

- Processes to memory
  - **Encoding or registration**: receiving, processing and combining of received information
  - **Consolidation**: stabilizing a memory trace after initial acquisition
  - **Storage**: creation of a permanent recorded of the encoded information
  - **Retrieval, recall, or recollection**: calling back the stored information in response to some cue for use in a process or activity

Sleep plays a vital role in encoding & consolidating memory
Sleep Deprivation

- Daytime ability to encode relies on medial temporal lobe & hippocampus
  - **Sleep deprivation** interferes with the normal communication b/w these areas of the brain
  - As compensation, prefrontal regions of brain assist and facilitate recruitment of the parietal lobe

Clinical correlate ➔ *Those with pre-existing prefrontal lobe dysfunction are more sensitive to effects of sleep deprivation (depression, CVA).*

- Nature 2005; 437: 1272-8
- Neuropsychopharmacology 2001; 25: S68-73
- Curr Biol 2007; 17: R87
Sleep Deprivation

• Sleep deprived subjects
  – Poor performance on memory tasks
  – Effect continued in subgroup despite caffeine
  – Poor insight on performance – don’t even realize they perform poorly!

  *QJ Exp Psychol 2000; 53:271-9*

• Sleep is important for optimal cognitive function and learning
  – Functional MRI clearly contrasts sleep-deprived vs. well rested brains

  *Curr Opin Neurol 2008; 21(4):417-23*
Sleep and Learning

• Sleep after learning important ➔ Consolidation of information
  – Memory integration takes time to develop, requires slow ‘offline’ associative processes
    Proc Natl Acad Sci USA 2007;102:7723-8
  – Sleeping after exposure to a problem: 2x more likely to solve
  – Evidence of **selective rehearsing** more difficult aspects of task
    Nat Neurosci 2000; 3(12):1237-8;

➔ During sleep, the brain replays collections of memories to discover patterns & thus help find meaning in what has been learned.
Study, then Sleep

Slow Wave Sleep is the key

- Slow wave sleep (SWS) – Critical role for consolidation of episodic facts. Nature 2006; 444:610-13
- Memories after night of sleep are more resistant to interference. Curr Biol 2006; 16: 1290-4
- ‘Perfume’ experiments on learners. Science 2007; 315 (5817): 1426-9
- PET scan experiments – Daytime learning produces hippocampal activity – Re-emergence of hippocampal activation during deep, SWS
- Amount of SWS reactivation in the hippocampus was proportional to next day task improvement. Neuron 2004; 44:535-45
Study, then Sleep

• Slow wave sleep (SWS) plays critical role in consolidation
  - Memories after night of sleep are more resistant to interference.
  - Proposed mechanism: Reactivation of memory representations during SWS and possibly REM sleep
  - ‘Perfume’ experiments on learners
  - PET scan experiments
    • Daytime learning produces activity in the hippocampus
    • Re-emergence of same hippocampal activation during deep, SWS
    • Amt of SWS reactivation in the hippocampus was proportional to next-day improvement

Nature 2006; 444:610-13
Curr Biol 2006; 16: 1290-4
Science 1994; 265: 676-9
Nat Neurosci 2007; 10: 100-7
Science 2007; 315 (5817): 1426-9
Neuron 2004; 44:535-45
Practice, then Sleep

It’s all about the spindles
Practice, then Sleep

• NREM 2 important for procedural learning
  – Spindle density increased after intensive training on a pursuit motor skill task & after combined training on several simple procedural motor tasks.
    

  – Mechanism: Spindles stimulate the brain to facilitate long term synaptic strengthening essential for memory consolidation
    
    Psychologica Belgica 2004; 44:81-104
Stress, then Sleep

... the eyes have it.
Neuroplasticity: 

*Sleep to Remember & Forget*

- Sleep plays an active role in modulating synaptic plasticity
  - Local sleep dependent neural pruning
  - Highly specific anatomic levels
  - Rescales synaptic strength which leaves behind more efficient, refined memories
  - Next day improved recall

  *Sleep Med Rev 2006; 10:49-62*

- Sleep deprivation inhibits synaptic plasticity and adult neurogenesis
  - Prolonged sleep deprivation may underlie cognitive deficits

  *Proc Natl Acad Sci USA 2006; 103 (50)19170-5*

- **Amyloid plaques:** earlier & more abundant in sleep dep. mice
  - ? Link between sleep disruption and subsequent development of dementia.

  *Kang et al. Science 2009*
Stress, then Sleep

• REM sleep important in emotional memory processing
  – Experiences that evoke emotions encode more strongly, persist longer
  – During REM, increased activity within limbic and paralimbic structures (hippocampus, amygdala)

Ann NY Acad Sci 2009; 1156:168-97

– Dreams allow integration & understanding of recently experienced emotional events in context of pre-existing memories

Nat Rev Neurosci 2002; 3:591-605

• REM sleep may aid in the resolution of previous emotional conflict, resulting in improved next-day negative mood.

Psychiatry Res 2006; 141:261-70
Sleep Disorders in the Elderly

- Sleep disorders become more common as we age
  - ↑ Prevalence for insomnia, OSA, RLS, and REM behavior disorder

- Pharmacological agents more prone to side effects in the elderly
  - ↑ Risk for confusion, residual daytime effects, interactions with other meds, & intolerance due to medical conditions
    - E.g. *diphenhydramine* (Benadryl) with anticholinergic side effects has a ↑incidence of cognitive impairment & daytime sleepiness in elderly

- Paramount for medical professionals to correctly recognize and treat to help maximize cognition and brain health
Insomnia

- Insomnia as a symptom is a common problem reported by patients; however, the cause may have many roots:
  - Breathing related (e.g. OSA) 5%
  - Restless legs syndrome 5-10%
  - Insomnia assoc. with psychologic dx 40%
  - Psychophysio logic Insomnia 15-20%
  - Substances (alcohol, medications) 5%
  - Body clock problems (Owl/Lark/ Jet lag) 10%
  - Other 10-20%
Addressing Insomnia

• Evaluate the patient for potential causes of Sx that may be addressed directly:
  – Poor sleep hygiene
  – Psychological illnesses
  – Medical illnesses
  – Medication side effects
  – Sleep Apnea
  – Restless Legs syndrome

• Consider non-pharmacologic interventions for treatment first
  – Avoid pitfalls
  – General Recommendations / Sleep hygiene
  – GOLD STANDARD: Cognitive Behavioral Therapy for Insomnia
Potential Pitfalls

- Frequent daytime naps*
- Spending too much time in bed*
- Lack of consistent routine
- Insufficient daytime activities & exposure to light
- Excess caffeine
- Alcohol consumption

- Late, heavy dinner
- Watching TV in bedroom
- Anxiety or anticipation of poor sleep
- Clock watching
- Late evening exercise
- Environmental: noise, too warm, lights, pets, active or noisy bed partners
General Recommendations

• Keep a consistent bedtime/waketime routine on weekdays & weekends.
• Don’t go to bed unless sleepy.
• Limit time in bed (at most 9 hrs).
• Avoid daytime naps.
• Avoid watching television, reading for great length, eating or doing other activities in bed inconsistent with sleep.
• Attend to the environment to address noise disruptions, excess light, and adjust temperature.
• Avoid excess caffeine particularly in the afternoon or late in the day.
• Avoid alcohol use, particularly at night.

→ Frustrating part . . . Good sleep hygiene alone rarely corrects long term sleep dysfunction.
Cognitive Behavioral Therapy for Insomnia (CBT-I)

• What is it?
  – Gold standard method for treating insomnia without the use of sleeping pills
  – Goals:
    • Identify sleep habits, scheduling factors, and misconceptions about sleep that perpetuate insomnia
    • Develop and follow a plan to change
    • Techniques include stimulus-control, sleep restriction, cognitive therapy, relaxation
  – Regular, often weekly, visit to a clinician who will assess and advise (new online programs)

• CBT-I effective for chronic insomnia in the elderly, even in the setting of comorbid medical and psychological conditions
  – Superior to zopiclone (similar to eszopiclone) in RCT
    
    JAMA. 2006;295(24):2851-2858
Pharmacologic Agents for Sleep in the Elderly

- Consider chronic conditions leading to cognitive impairment, balance & gait difficulties
- Review other Rx’s of CNS active agents
  - Psychotropics & anticholinergic\'s may ↑ risk of cognitive toxicity
- Discuss risks and benefits of sedative hypnotics
- Start low and go slow
  - ½ recommended adult dose
Pharmacologic Agents for Sleep in the Elderly

- Limited data, modestly effective, well tolerated treatments with FDA approval:
  
  **Benzodiazepine Receptor Agonists**
  - Zolpidem *(Ambien)*: 5mg, dizziness, H/A 2.9 – 3.7 hr
  - Zolpidem ER *(Ambien CR)*: 6.25mg, dizziness, H/A 1.9 – 7.3 hr
  - Zaleplon *(Sonata)*: 5 mg nausea/ myalgias (7%), 1 hr
  - Eszopiclone *(Lunesta)*: 1-2 mg H/A, metallic taste 9 hr

  **Melatonin Receptor Agonist**
  - Ramelteon *(Rozerem)*: 8 mg H/A (7%), others even less 1-2.6 hr

  **Benzodiazepines**
  - Temazepam *(Restoril)*: 7.5-15mg 3.5-18.4 hr

- No systematic evidence for effectiveness of many medications and risks may outweigh benefits in this population
  - Antihistamines
  - Antipsychotics
  - Antidepressants
  - Anticonvulsants
“The good news, Mr. Phelps, is that you do not have apnea. The bad news is that Fluffy sleeps on your face.”
Obstructive Sleep Apnea (OSA)

- Repetitive collapse of the upper airway during sleep
- “Consequence of speech”
- Spectrum of disease
  - Pharyngeal vibration $\rightarrow$ Snoring
  - Flow limitation $\rightarrow$ Hypopnea
  - Cessation of flow $\rightarrow$ Apnea

Apnea Hypopnea Index (AHI)
- 5-15 Mild
- 15-30 Moderate
- >30 Severe
The Upper Airway Appearance of OSA
Overnight Sleep Study with OSA

Apnea Hypopnea Index (AHI)
- 5-15  Mild
- 15-30  Moderate
- >30  Severe

Obstructive Apnea

Supine

Pressure (-5.8)

SaO2 (83.3)

Min 70.0
Consequences of Untreated OSA

- Impaired cognitive function
- Impaired quality of life
- Daytime sleepiness
- Increased risk of automobile accidents
- Cardiovascular disease
- Hypertension
- Worsened glucose tolerance -> Development of DM?
- Impotence
- Increased mortality rates
- Increased health care costs
- Loss of societal productivity

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Economic Effects

Consequences of Untreated OSA

- Impaired cognitive function
  - Impaired quality of life
  - Daytime sleepiness
  - Increased risk of automobile accidents
  - Cardiovascular disease
  - Hypertension
  - Worsened glucose tolerance -> Development of DM?
  - Impotence
  - Increased mortality rates
  - Increased health care costs
  - Loss of societal productivity

OSA in the Elderly

- For the middle aged, risk factors for OSA help to determine propensity for disease
  - RF’s: h/o snoring, obesity, large neck size, h/o HTN, male
  - 2% of women & 4% of men in 1990’s aged 30-60 yr
  - Likely higher now due to rise in obesity

- OSA ‘age dependent’ with ↑ prevalence with age
  - Up to 44% demonstrate moderate OSA (AHI > 20/hr)
  - SHHS: 18% (AHI > 15)
    - Mean age 63.5
    - N= 1780 > 70, plateau effect at that age
  - CPS: Men 13.3% (AHI > 20), Women 7.2% (AHI >15)
    - Ages 65-100 yrs
  - Less reliance on RF, e.g. reports of snoring may be less
OSA in the Elderly

• Cleveland Family Study
  – Detailed analyses of longitudinal changes of OSA incidence
  – AHI increased by 30-40% over a 5 yr f/u
  – Extent of change was dependent on age, sex, and BMI
    • 60 y/o, BMI of 30, increase in AHI over 5 yrs
      – Men → ↑ AHI of 3.6 /hr
      – Women → ↑ AHI of 1.6 /hr
    • Steeper ↑ rates associated with higher baseline BMI, being male, & older baseline age
Populations at Higher Risk of SDB

- Congestive heart failure
- Atrial fibrillation
- Treatment refractory hypertension
- Type 2 diabetes
- Nocturnal dysrhythmias
- Stroke
- Pulmonary hypertension
- Obesity (BMI > 35)
- High-risk driving populations
- Preoperative for bariatric surgery
OSA in the Elderly

• If OSA is so common, are the consequences in the elderly any less than that in the middle aged?

• Is the necessity or threshold to treat different for the elderly?
OSA Stress on Brain Cells

- **Chronic sleep fragmentation & hypoxemia**
  - Disrupts cellular and chemical homeostasis, restorative processes
  - Chain reaction may lead to altered neuronal and glial viability
    
    J Int Neuropsychol Soc 2004, 10(5);772-85

- **Animal models:** Sleep apnea increases neuronal apoptosis (death) in hippocampus and overlying cortical region.
  
  J Sleep Res 2002;11(1)1-16

- **Human studies:** Relationship between degree of hypoxemia, frequency of resp events, and resulting cognitive dysfunction.
  - **Hypoxemia** → affect tests of global cognitive function
  - **Sleep fragmentation and arousal** → affects tests of attention and vigilance
    
    J Int Neuropsychol Soc 2004, 10(5);772-85
    Sleep 1998;21(4):392-7
    J Clin Exp Neuropsychol 1996;18(2)197-210
OSA and Stroke

• Changes in cerebral perfusion seen with OSA
  Pneumologie 1997; 51(9)926-3

• OSA is a risk factor for stroke
  AJCCM 2001; 163 (1); 19-25
  – Pre-stroke white matter changes were seen & predicted the occurrence of more white matter changes with time
  Neurology 2003; 61(7) :959-63
  – May translate to higher rates of vascular dementia in pts with OSA
OSA impairs Cognitive Function

• OSA may lead to permanent injury to CNS
  – Grey matter loss in frontal cortex, parietal cortex, temporal lobe, anterior cingulate, and hippocampus on MRI
  – Hippocampal loss and atrophy in OSA pts on MRI
  – Metabolic changes in the brain compared to controls despite treatment (MR spectroscopy)
  – White matter changes in the limbic system, cortex, and the projections to and from the cerebellum. (Diffusion tensor imaging of MR)

2. AJRCCM 2002; 166:1382-7
4. Sleep 200730(3)305-11
5. Sleep 2008; 31(7)967-77

• Similar to early stages of dementia
  – Sustained attention problematic → Performance worse as task lengthens.
  – Poor performance on tests of executive function
    • Difficulties with planning, sequential thinking, & constructional ability
  – Decreases in overall intelligence and language
  – Memory deficits

Sleep 2003; 26(3)298-307; Sleep Med Reviews 2001; 5(3) 223-36; J Int Neuropsychol Soc 2004, 10(5);772-85; Chest 1986; 90(5) 686-90; J Clin Exp Neuropsychol 1991;13(6);950-64
OSA and Dementia

- OSA aggravates cognitive dysfunction in pts with dementia
  - Possible **reversible** cause of cognitive loss in those with Alzheimer’s disease.
    
    J Am Geriatri Soc 2006;54(5):777-81

  - CPAP reduces subjective daytime sleepiness in patients with Alzheimer’s disease and OSA.
    

  - Small study showed **slowing** of cognitive deterioration in those with OSA and Alzheimer’s dementia
    • Those who were able to use CPAP vs. those who could not
      
Benefits of PAP Therapy

- Improved alertness/ decreased sleepiness
- Increased reaction times, better memory
- Improved driving ability
- Decreased depression and anxiety
- Decreased risk of stroke, deaths from cardiovascular disease
- Improved BP control

OSA and the Elderly

- Evidence would suggest treatment of OSA in the elderly is as important as in a younger group
  - To maintain cognitive function in the healthy
  - To slow progression in those with dementing illness
  - To improve sleep quality and help avoid pharmacologic agents
  - To improve of daytimes symptoms that may impact quality of life
Conclusions

- Sleep plays a crucial role in cognitive function including memory, learning, and regulating emotions.
- As we age, fundamental changes to the mechanisms of sleep occur leading to increased sleep disruption.
- Sleep disorders are common in the elderly, but may be difficult to separate from normal aging and the effects of comorbid conditions.
- Untreated sleep disorders may significantly impact cognition.
- OSA diagnosis and treatment may help improve cognitive complaints, slow progression of dementia.
Recommended Readings


• Evidence based recommendations for the assessment and management of sleep disorders in older persons, Bloom et al., *JAGS* (2009) S7:761-789

