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New concepts in Alzheimer's Cause, Progression and Therapy

### Why sleep should not be ignored in Alzheimer's Disease



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### Conflict of Interest Disclosures Presenter: Bryce Mander

1. The authors do not have any potential conflicts of interest to disclose, **OR** 

2. The authors wish to disclose the following potential conflicts of interest:

| Type of Potential Conflict | Details of Potential Conflict |
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## What Causes Unsuccessful Cognitive Aging?



Time (Years) —

### **Could sleep disturbance be one factor?**



# Sleep in Young and Older Adults



# Sleep in Mild Cognitive Impairment

Normal ControlsaMCI Patients



In aMCI, SWS and REM sleep are reduced and sleep is more fragmented

#### Adapted from Westerberg et al, 2012 and Hita-Yanez et al, 2012

# Sleep in Alzheimer's Disease



# **Common Sleep Disorders**



### Sleep-related breathing disorders

- Obstructive sleep apnea (OSA) most common form
  - Caused by obstruction, usually in upper airway
  - Causes repeated intermittent hypoxia and sleep fragmentation
  - Severity Quantified by AHI and RDI (Thresholds: AHI >5, RDI >15)
  - Continuous positive airway pressure (CPAP) most common treatment

### Insomnia

- Defined as "a repeated difficulty with sleep initiation, duration, consolidation, or quality that occurs despite the adequate opportunity and circumstances for sleep, and results in some form of daytime impairment."
- Many forms, causes, and theoretical mechanisms
- Cognitive Behavioral Therapy for insomnia (CBT-i) is the recommended first line treatment

#### From ICSD-3 by AASM, 2014



Sleep disorders more likely with

- Medical comorbities
- Psychiatric conditions

- Sleep disorders increase
  - Mortality risk
  - Risk for cognitive decline

 In dementia, >60% have 1+ sleep disorder
 Guarnieri et al, 2002, Guarnieri et al, 2012, & Ancoli-Israel et al, 1991 and 2009

# AD and Sleep Disorders: Direct Paths







Li et al, 2016, & Nagayoshi et al, 2016

### Poor sleep quality increases AD risk



From Lim et al, 2013b

# Good sleep quality reduces APOE4+ AD risk

Figure 1. Apolipoprotein E (APOE) Genotype, Sleep Consolidation, Cumulative Incidence of Alzheimer Disease, and Rate of Cognitive Decline



From Lim et al, 2013a

# Aβ and sleep



**Sleep Duration** 6-7hr >7hr <6hr **MNI** Template



#### Spira et al, 2013

Kang et al, 2009

# Aβ and slow waves before MCI?

# Cortical generators of NREM slow waves



#### β-amyloid pathology



Buckner et al, 2005

## Aβ effects on SWA in healthy controls



*Aβ* deposition disrupts SWA <1Hz within mPFC

#### From Mander et al, 2015

### Does SWA explain Aβ impact on memory?



mPFC SWA <1Hz predicts overnight memory retention

#### From Mander et al, 2015

# Summary



- In AD, sleep disruption and disorders are prevalent
- Sleep disruption and disorders worsen as AD progresses
- Before MCI & AD, sleep disruption and disorders increases risk
- Specific forms of sleep disruption track
  - AD pathology before MCI onset
  - Cognitive impairment and decline
- Treating sleep disturbance may
  - Delay MCI onset
  - Improve cognitive impairment in the elderly and dementia patients

### Could sleep aid early detection and prevention?



#### Matt Walker, PhD

#### Walkerlab

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"Mr. Osborne, may I be excused? My brain is full."

Sleep Well...!



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# **EXTRA SLIDES**

# Sleep in Alzheimer's Disease



From Prinz et al, 1982

# Aβ effects on SWA distinct from normal aging?



Carrier et al, 2011

### Path analysis models details



#### From Mander et al, 2015

### What can patients and care-givers do about it? Recommendations from the National Sleep Foundation

- If you have sleep problems, talk to your doctor about it!
- Tell doctors managing cognitive symptoms about sleep problems
- Practice good sleep hygiene as a patient and caregiver
  - No caffeine after early afternoon, no more than 1 nap
- Keep a very regular sleep/wake schedule
- Bright light soon after waking, dim light at night
   Use a red nightlight!
- Stay active, both in mind and body
  - Exercise at least a little every day, combine with learning
- If you are a caregiver, get help
  - Overnight help reduces burden dramatically
  - Get emotional support
  - Have your own social life
  - Get enough rest



### What are we doing about it? Experimental methods to enhance slow wave sleep

- Treating sleep disorders, monitoring outcomes
- Pharmacology (Mostly GABAergic)
- Transcranial direct and alternating current stimulation (tDCS & tACS)
- Transcranial Magnetic Stimulation (TMS)
- Vestibular stimulation via slow rocking
- Acoustic stimulation timed to slow waves

### The Cascade Hypothesis of Alzheimer's Disease



From Jack et al, 2013

### Path Analysis Models



*mPFC* Aβ influences memory through SWA in healthy older adults

#### From Mander et al, 2015