Sleep circadian rhythms, and the pathogenesis of Alzheimer disease

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INTRODUCTION

- Disturbances in the sleep–wake cycle and circadian rhythms are common symptoms of Alzheimer Disease (AD), and they have generally been considered as late consequences of the neurodegenerative processes
- Recent evidence demonstrates that sleep–wake and circadian disruption often occur early in the course of the disease and may even precede the development of cognitive symptoms

INTRODUCTION

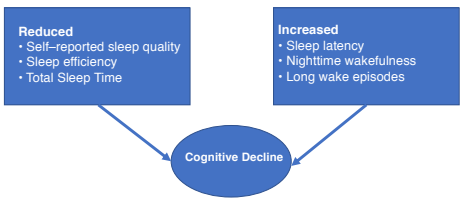
- Sleep–wake cycle appears to regulate levels of the pathogenic amyloid-beta peptide in the brain, and manipulating sleep can influence AD-related pathology in mouse models via multiple mechanisms
- Circadian clock system, which controls the sleep–wake cycle and other diurnal oscillations in mice and humans, may also have a role in neurodegenerative process

Sleep is essential for brain functioning

- Wakefulness
  - Alertness: increases 20% of brain energy consumption during the day
  - Learning: neural synapses require energy and space
- Sleep
  - "Re-organize": switch off external inputs and erase unneeded neural nets
  - "Re-charge": restore brain energy (glycogen)
  - "Consolidate memory": preserve crucial neural networks, store long term memory

Tononi, Sleep Med Rev. 2006.

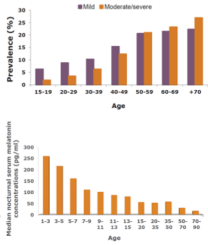
Poor sleep leads to cognitive decline line in healthy cognitively impaired and demented



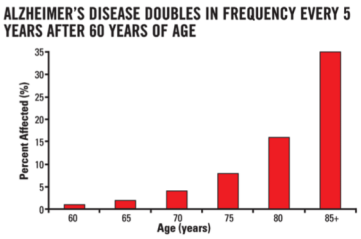
Miyata et al., J Sleep Res 2013; McKinnon et al. J Geriatr Psychiatry Neurol. 2014; Vitiello et al., J Gerontol. 1990; Carpenter et al., Clin. Gerontologist 1996, McCurry et al., J Geriatr Psychiatry Neurol,1999

Relationship between age, production of melatonin and prevalence of insomnia

- Melatonin is the physiological regulator of sleep and the circadian clock
- As we age (50+), the biological clock function declines and melatonin production is reduced.
- ~50% of the 55+ population report insomnia and an overall of sleep.



Prevalence of Alzheimer's Disease by age



Cummings JL. Primary Psychiatry. Vol 15, No 2, 2008

Prevalence of Alzheimer's Disease

- One in nine individuals (11%) aged 65 and older has Alzheimer's disease.
- About one-third of people aged 85 and older (32%) have Alzheimer's disease.
- Of those with Alzheimer's disease, the vast majority (82%) are aged 75 or older

Hebert et al Neurology 2013

Risk factors for Alzheimer's Disease

- Age
- Family history and genetics
- Gender
- MCI (Mild Cognitive Impairment)
- Poor sleep quality
- Lack of exercise
- High blood pressure
- Smoking

Marcello et al. Eur J Pharmacol. 2008; Nimmrich & Ebert, Rev Neurosci. 2009; Selkoe, Nat Med. 2011; Osorio J Am Geriatr Soc. 2011

Prevalence of Insomnia in AD patients

- 55% of adults 65 years and older have at least one chronic sleep complaint.
- Sleep disturbances in AD affecting up to 45% of the patients. These disturbances are similar in nature to adults without AD
- Nighttime awakenings are common in AD, affecting caregivers quality of life and can lead to nursing home placement
- Acetyl-cholinesterase (AChE) inhibitors cause sleep disturbances in 14% of patients and daytime fatigue in 5% of patients
- Altogether 1 out of 2 AD patients suffers from insomnia

Foley et al. Sleep. 1995; Landry & Liu-Ambrose Front. Aging Neurosci. 2014; Osorio et al J Am Geriatr Soc. 2011

Insomnia in AD patients

- There is a strong association between objective and subjective measurements of sleep and subsequent cognitive decline
- Poor sleep and specifically the inability to sustain extended periods of both sleep and wakefulness exacerbate 'age-related' cognitive decline.
- A significant correlation between disrupted SWS and increased plasma levels of amyloid-beta was demonstrated-suggesting causality between poor sleep and the subsequent cognitive decline

Diekelmann & Born, Nat Rev Neurosci 2010; Swearer et al. J Am Geriatr Soc., 1988; Altena et al. Prog Brain Res., 2010; Chavant et al. Br J Clin Pharmacol., 2011; Spira et al. JAMA Neurology, 2013; Pollak et al. J Geriatr Psychiatry Neurol. 1991

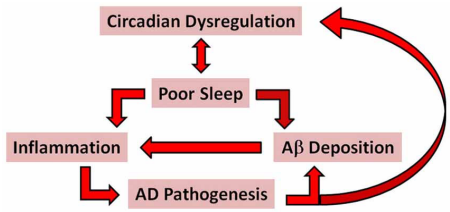
Beta-amyloid and Sleep

- Beta-amyloid (Aβ) is present in the brain's interstitial fluid (ISF) and is considered a metabolic "waste product"
  - Mechanisms by which Aβ is cleared from the brain are not completely understood
  - Evidence that sleep plays an important role in Aβ clearance
  - In rodents, chronic sleep restriction led to increases in ISF Aβ levels
  - In a *Drosophila* model of Alzheimer's disease (AD), chronic sleep deprivation (SD) resulted in higher Aβ accumulation

Beta-amyloid and Sleep

- In healthy humans, imaging studies have revealed associations between self-reports of less sleep duration or poor sleep quality and higher Aβ burden (ABB) in the brain, which is a risk factor for AD
- Bidirectional association, increased ABB could also lead to impairments in sleep
- Notably, increased ABB in the brain associated with impairment of brain function
  - Thus, strategies prevent Aβ accumulation in the brain could promote healthy brain aging and be useful in preventing AD
  - Increasing evidence that sleep disturbances might contribute to AD, in part by facilitating accumulation of Aβ in the brain

Causal relationship between insomnia and AD



Landry & Liu-Ambrose Front. Aging Neurosci. 2014

Poor sleep is causally liked to cognitive decline in AD

- Among community-dwelling older adults, reports of shorter sleep duration and poorer sleep quality are associated with greater Aβ burden
- Amyloid is produced while brain activity is increased; excess is cleared away by the glymphatic system when asleep
- Poor sleep may promote Aβ deposition and exacerbate loss of cognitive function
- Decrease in brain activity during night sleep is essential for amyloid clearance in AD related areas such as the precuneus
- The precuneus is most sensitive to poor quality of sleep

Blackwell et al. Sleep 2014; Miyata et al., J Sleep Res 2013; Murre et al. Memory 2014; Lim et al. JAMA Neurol, 2013; Sanchez-Espinosa Neuroimage, 2014; Malkki Nature Rev Neurol, 2014; L ucey et al. Neurobiology of Aging, 2014

Why should we treat insomnia in AD patients?

- Presence of insomnia is significantly associated with AD (odds ratio (OR) = 3.32, 95% CI = 1.33–8.28).
- In AD patients with insomnia comorbidity, dementia tends to be more severe and progress faster
- A recent fruit-fly study suggests 'extra sleep' may stall Alzheimer's disease
- Interventions to improve sleep among older adults may ameliorate Aβ burden and slow down the sleep-related AD onset and progression

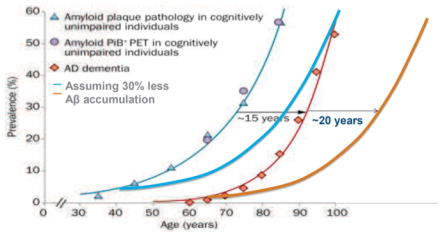
Osorio J Am Geriatr Soc. 2011; Blackwell et al. Sleep 2014; Carpenter et al., Clin. Gerontologist 1996, McCurry et al., J Geriatr Psychiatry Neurol,1999 Lucey et al. Neurobiology of Aging, 2014; Dissel et al Current Biology , 2015

Sleep disorders in AD are misperceived

- Generally regarded as
  - A normal signs of aging
  - At a later stage "sundowning" becomes a secondary symptom to the disease
- Should be regarded as
  - A major risk factor to AD
  - A comorbidity that ultimately brings about faster deterioration in cognition and function

Osorio J Am Geriatr Soc. 2011

Improving sleep: Buying time



Modified from Langbaum et al Nat Rev Neurol. 2013; Osorio J Am Geriatr Soc. 2011

THE SLEEP– WAKE CYCLE AS A MODULATOR OF AD PATHOGENESIS

THE SLEEP– WAKE CYCLE AS A MODULATOR OF AD PATHOGENESIS

- Sleep disturbances are a common feature of AD and are observed in mouse AD models
- AD patients exhibit disturbances in the timing and duration of the sleep cycle, primarily manifested as increased wakefulness at night (due to increased sleep latency and increased nocturnal awakenings) and increased sleep during the day

THE SLEEP– WAKE CYCLE AS A MODULATOR OF AD PATHOGENESIS

- In terms of sleep architecture
  - Duration of rapid eye movement (REM) sleep bouts is decreased in AD patients compared with age-matched controls
  - Slow-wave sleep also diminished in AD.
- Several studies in transgenic mice demonstrate that amyloid deposition in the brain (and in some cases tau aggregation) leads to the disruption of normal sleep architecture, an effect that often precedes the appearance of amyloid plaques.
  - Abnormalities in mice include a loss of robust day– night oscillation in brain lactate,8 phase delay, altered nocturnal activity level,and decreased non-REM sleep

Sleep disturbances may predict dementia and Aβ pathology

- Sleep disturbances may be early indicators of dementia and Aβ pathology and may actually precede the onset of cognitive symptoms in AD
- Using actigraphy shown to be a good surrogate marker for sleep
- Fragmentation of sleep, which can be quantified using actigraphic data to analyze the frequency and duration of runs of uninterrupted rest during the night, may be an indicator or arbiter of cognitive impairment

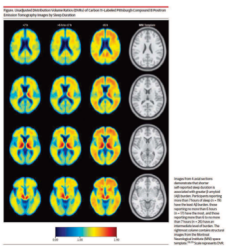
Sleep disturbances may predict dementia and Aβ pathology

- Rest fragmentation at night increases with age and is associated with 1.5-fold increased risk of developing dementia in the ensuing 6-year follow-up period
- Several studies have examined the relationship between sleep quality and Aβ pathology in cognitively normal older adults.
  - Using actigraphy to assess sleep parameters, found that cognitively normal adults with cerebral Aβ deposition on amyloid (PET) (PiB) imaging were more likely to nap frequently and had significantly worse sleep efficiency than those without PiB-positive plaques.

Ju et al.23

Self-reported Sleep cause β-Amyloid Deposition in Older adults

- After adjustment for potential confounders
  - Shorter sleep duration was associated with greater Aβ burden, as measured by mean cortical DVR (B = 0.08 [95%CI, 0.03-0.14]; P = .005) and Precuneus DVR (B = 0.11 [0.03-0.18]; P = .007).
  - Lower sleep quality was associated with greater Aβ burden, as measured by Precuneus DVR (B = 0.08 [0.01-0.15]; P =.03).



Spira et al. JAMA Neurology, 2013

Sleep disturbances may predict dementia and Aβ pathology

- Presymptomatic amyloid deposition affects sleep and suggest that specific alterations in sleep or activity parameters might be an early biomarker of impending AD

Control of Aβ levels by the sleep–wake cycle

- Using in vivo cerebral microdialysis, a method in which brain interstitial fluid (ISF) from brain regions such as the hippocampus
  - ISF Aβ levels demonstrate diurnal rhythm
  - Levels of Aβ were highest during the dark phase (awake) and lowest during the light phase (asleep)
  - Increased neuronal activity during wake phase might mediate the diurnal increase in Aβ.
    - Slow wave sleep associated with a period of neuronal hyperpolarization and diminished neuronal firing and associated with less Aβ production

Kang et al.

Sleep deprivation exacerbates Aβ pathology

- Forced sleep deprivation caused a striking increase in the Aβ plaque burden in transgenic mice that express AD- associated mutant forms of human amyloid precursor protein (APP) and presenilin-1 (PS1) and develop Aβ plaques with age
- Conversely, treatment with the orexin antagonist almorexant, which increased sleep, decreased plaque burden

Kang et al.

Sleep deprivation exacerbates Aβ pathology

- **β-Amyloid accumulation in the human brain after one night of sleep deprivation**
  - Using positron emission tomography show that acute sleep deprivation impacts β-amyloid burden in brain regions that have been implicated in Alzheimer's disease
  - Provide preliminary evidence for the negative effect of sleep deprivation on β-amyloid burden in the human brain

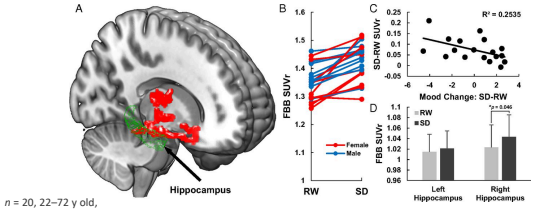
Ehsan Shokri-Kojori et al, 2017

Sleep deprivation exacerbates Aβ pathology

- One night of sleep deprivation, relative to baseline, resulted in a significant increase in Aβ burden in the right hippocampus and thalamus
- Baseline ABB in a range of subcortical regions and the precuneus was inversely associated with reported night sleep hours.

Ehsan Shokri-Kojori et al, 2017

Sleep deprivation exacerbates Aβ pathology



n = 20, 22–72 y old,

^{18}F-florbetaben (FBB) PET

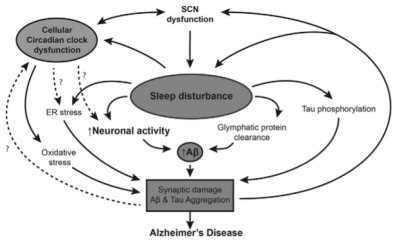
Ehsan Shokri-Kojori et al, 2017

Sleep deprivation mediates Aβ - independent neuronal injury

- Several studies have demonstrated that sleep deprivation can exacerbate neuronal injury via several mechanisms. For example,
  - Sleep deprivation can induce tau phosphorylation, synaptic injury, and impaired learning and memory in mice expressing mutant human tau, APP, and PS1 transgenes
- A night of sleep deprivation led to a 20% increase in CSF levels of neuronspecific enolase and SB-100, two markers of neuronal injury
- Sleep deprivation shown cause mitochondrial oxidative stress in wake-promoting neurons of locus ceruleus

Ehsan Shokri-Kojori et al, 2017

Mechanisms linking sleep deprivation, circadian dysfunction, and AD



CIRCADIAN DYSFUNCTION IN AD PATHOGENESIS

Circadian rhythms are critical to human health

- The SCN serves as the master body clock, which synchronizes these peripheral oscillators into coherent whole-organism rhythms that are in synch with external light– dark
- The circadian clock serves as a master integrator of cellular metabolism in peripheral tissue
- Circadian dysfunction has been implicated in the pathogenesis of aging and several disease states, including atherosclerosis, diabetes, and cancer

Interplay between sleep– wake cycle and circadian rhythms

- Sleep is clearly regulated by the circadian clock, as human sleep patterns follow clear circadian patterns
  - Deletion of master clock gene Bmal1 abrogates all circadian function leading to a total loss of day– night rhythmicity of sleep
- Sleep deprivation can alter expression of clock genes and DNA binding patterns of BMAL1/CLOCK heterodimers, thus altering clock function

Circadian dysfunction is a common symptom of Alzheimer disease

- Dysfunction and degeneration of the SCN lies at the root of the circadian dysfunction in AD
- Epidemiological data show that impaired systemic circadian rhythms in cognitively normal adults, as assessed by actigraphy, are significant risk factor for the future development of AD
- Diurnal oscillations in Aβ could be considered to have a circadian rhythm and could be mediated by upstream influences of the circadian system

Circadian clock gene deletion causes neuronal injury

- Mice with a brain-specific deletion of master clock gene Bmal1 in the cortex and hippocampus but with SCN spared,
  - thus leaving systemic circadian rhythms and sleep– wake cycle intact in the animal while completely disrupting circadian transcriptional regulation in the rest of the brain
  - Bmal1 knockout mice developed severe cortical astrogliosis, oxidative damage, and synaptic degeneration

In summary

- Circadian dysfunction occurs in AD and may precede symptom onset.
- The circadian clock may have a key role in regulating the expression of neuroprotective proteins and preventing cerebral oxidative stress and synaptic damage
- As a key regulator of the sleep– wake cycle, the circadian clock could also potentially contribute to the regulation of Aβ