Washington University in St. Louis
School of Medicine

Knight ADRC
Alzheimer's Disease Research Center
Washington University St. Louis

Sleep and Circadian Rhythms in Alzheimer Disease

Erik S. Musiek, MD, PhD

Charlotte & Paul Hagemann Professor of Neurology
Co-Director, Center On Biological Rhythms And Sleep (COBRAS)
Washington University School of Medicine
St. Louis, MO, USA

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COBRAS
Center On Biological Rhythms And Sleep

Conflicts of Interest/Disclosures

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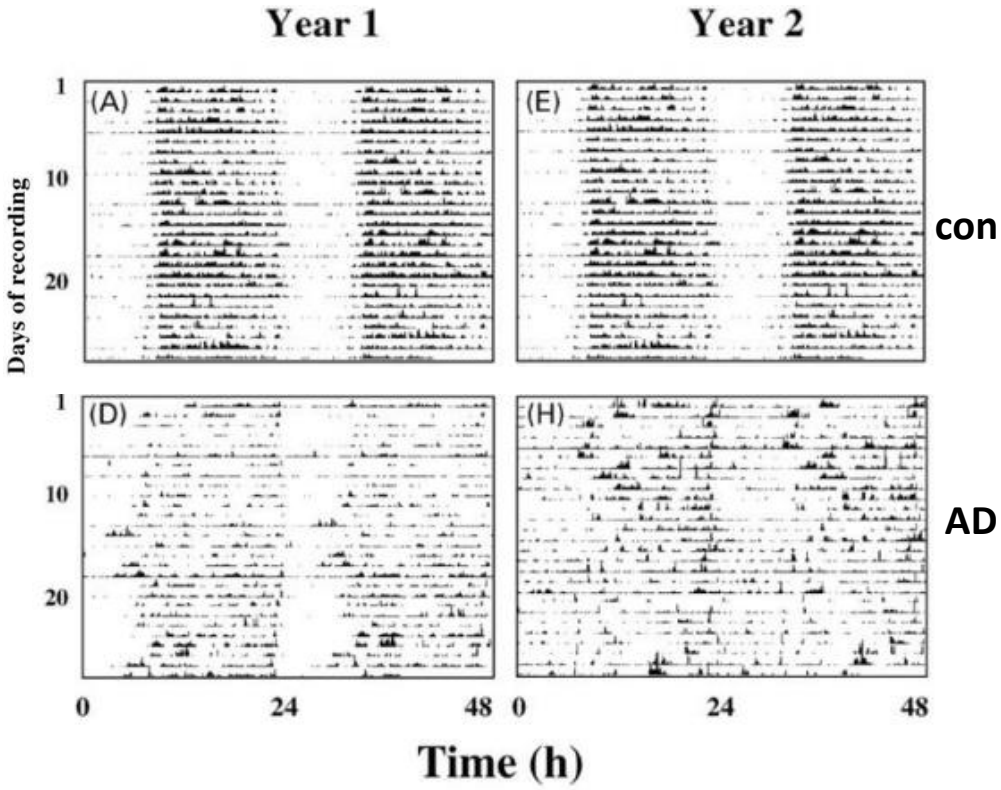
Sleep and circadian function is disrupted in symptomatic AD dementia

- Poor sleep efficiency
- Increased napping
- Decreased slow-wave sleep (NREM, <1hz)
- Decreased REM sleep
- Fragmented sleep-wake pattern
- Phase delay (~4 hrs)

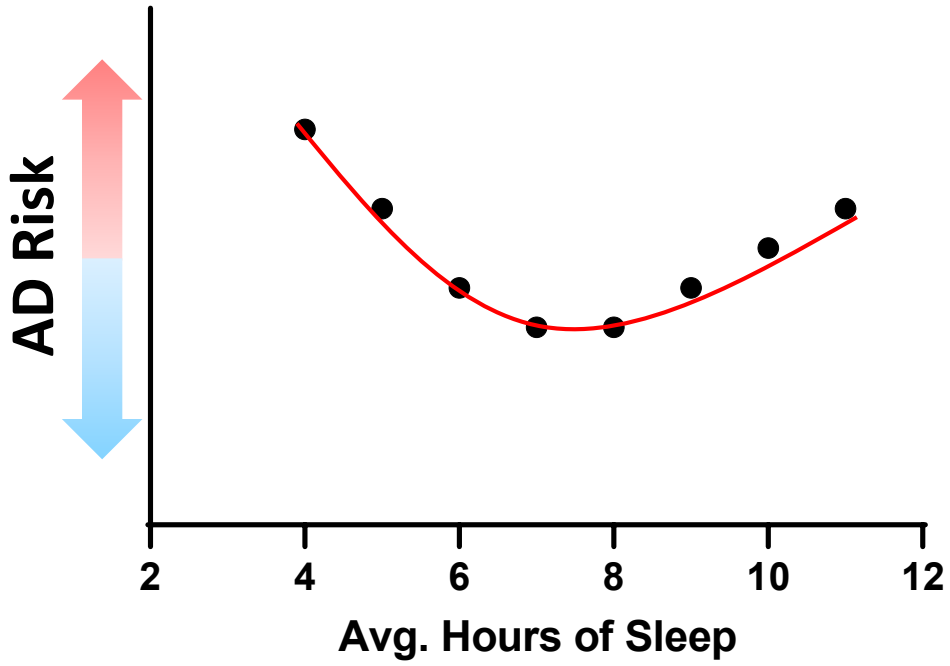
Source: *Scientific American*, May 2019



Hatfield et al. *Brain* 2004

Sleep duration and AD risk: U-shaped curve

- Short or long sleep are associated with increased AD risk.
- Most studies use self-reported sleep duration information.
- Few have AD biomarkers to confirm diagnosis or preclinical AD status.



Sabia S et al. *Nat Comm*, 2021

Westwood AJ et al. *Neurology*, 2017
Lutsey PL et al, *Alzheimer Dement*, 2017
Robbin R et al, *Aging*, 2021

Mid-life sleep influences dementia risk

nature communications

Article | Open Access | Published: 20 April 2021

Association of sleep duration in middle and old age with incidence of dementia

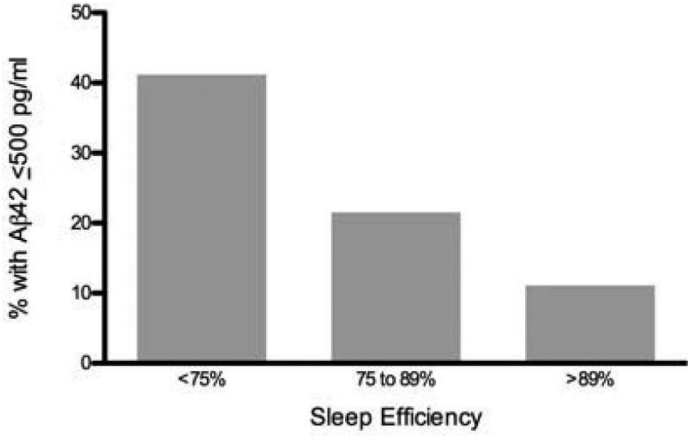
Séverine Sabia, Aurore Fayosse, Julien Dumurgier, Vincent T. van Hees, Claire Paquet, Andrew Sommerlad, Mika Kivimäki, Aline Dugravot & Archana Singh-Manoux

- Extremely long followup (25+ years) makes preclinical AD at first sleep assessment unlikely
- Self-reported sleep, no biomarkers

	N cases/*N* total	Incidence rate per 1000 persons-years	Model 1: adjusted for sociodemographic variables[a]	
			HR (95%CI)	*P* value[d]
Sleep duration at age 50[e]	521/7959			
Short: ≤6 h	211/3149	2.8 (2.4–3.2)	1.28 (1.06–1.55)	0.01
Normal: 7 h	219/3624	2.4 (2.1–2.7)	1 (ref.)	
Long: ≥8 h	91/1186	3.0 (2.4–3.7)	1.25 (0.98–1.59)	0.08
Sleep duration at age 60[e]	409/7164			
Short: ≤6 h	192/2759	4.7 (4.0–5.4)	1.48 (1.19–1.84)	<0.001
Normal: 7 h	142/2988	3.2 (2.7–3.7)	1 (ref.)	
Long: ≥8 h	75/1417	3.6 (2.8–4.4)	1.15 (0.87–1.52)	0.33

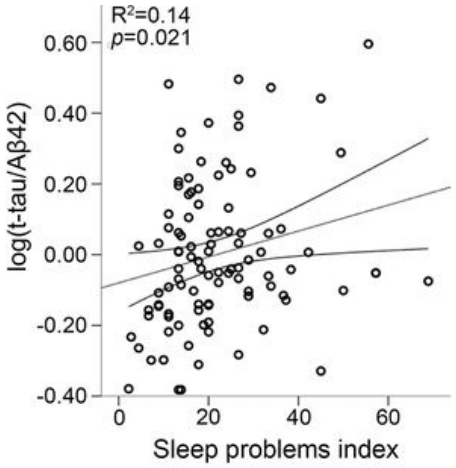
Preclinical AD pathology associated with sleep changes

Cognitively normal, CSF biomarkers, actigraphy



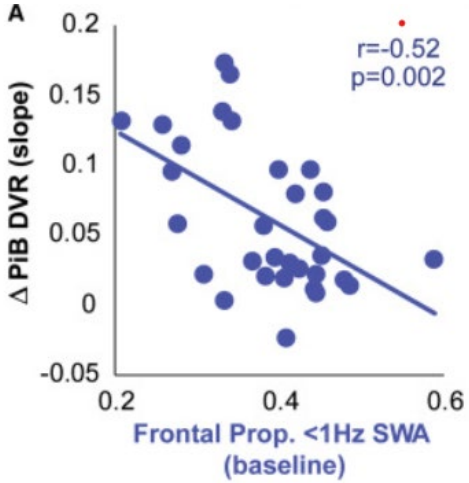
Ju YE et al, JAMA *Neurol*, 2013

Cognitively normal, CSF biomarkers, sleep questionnaire



Sprecher KE et al. *Neurology,* 2017

Cognitively normal, PSG, Amyloid PET imaging



Winer J et al. *Curr Biol,* 2020

In general, preclinical AD pathology (CSF or PET biomarker+) is associated with increased sleep latency, sleep fragmentation, increased WASO, decreased sleep efficiency, increased naps

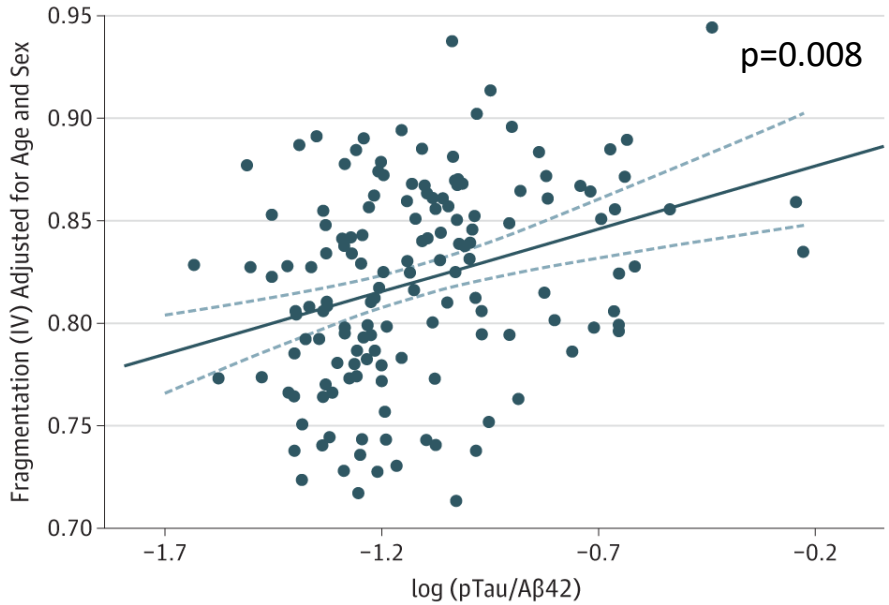
Ettore E et al., *Sleep*, 2019
Brown BM et al., *Sleep*, 2016
Branger P et al. *Neurobiol Aging, 2016*
Insel P*, JAMA Open,* 2021
Spira AP, *Sleep*, 2018

Circadian dysfunction precedes cognitive symptoms in AD

JAMA Neurology | Original Investigation

Circadian Rest-Activity Pattern Changes in Aging and Preclinical Alzheimer Disease

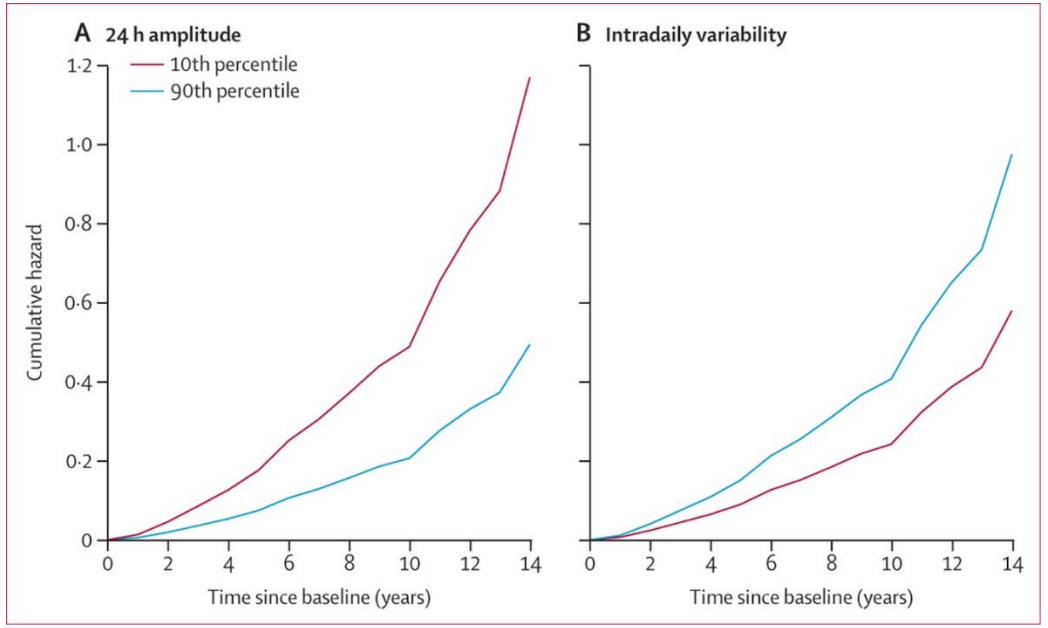
Erik S. Musiek, MD, PhD; Meghana Bhimasani, BS; Margaret A. Zangrilli; John C. Morris, MD; David M. Holtzman, MD; Yo-El S. Ju, MD



THE LANCET Healthy Longevity

Circadian disturbances in Alzheimer's disease progression: a prospective observational cohort study of community-based older adults

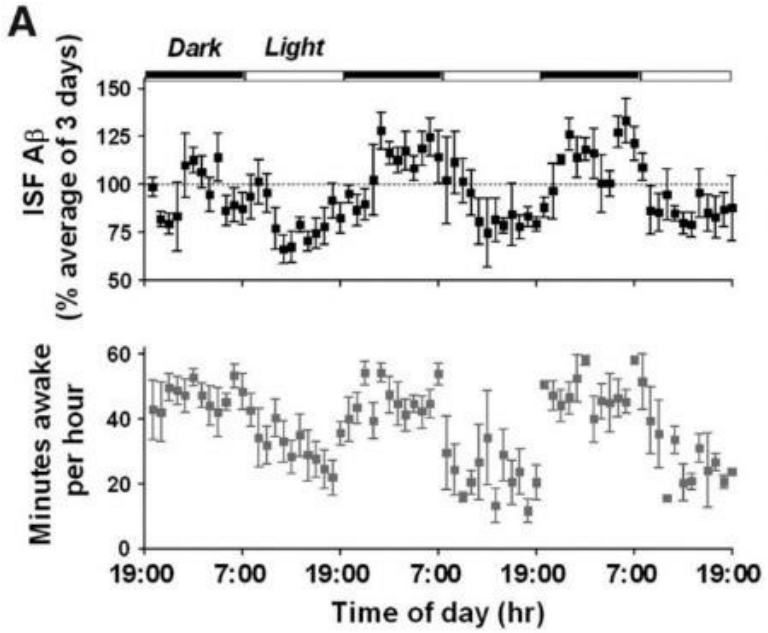
Peng Li, Lei Gao, Arlen Gaba, Lei Yu, Longchang Cui, Wenqing Fan, Andrew S P Lim, David A Bennett, Aron S Buchman, Kun Hu

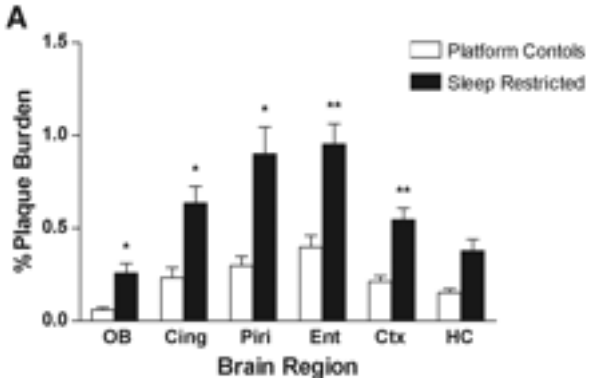


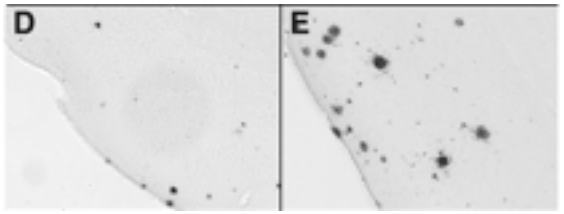
Li P et al. *Lancet Healthy Longev,* 2020

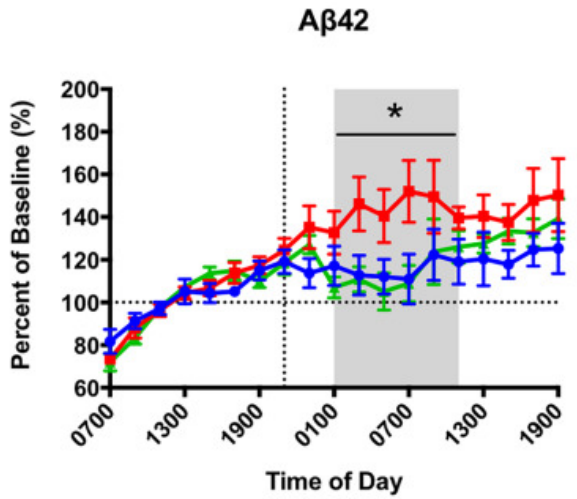
Sleep regulates Amyloid-β levels in mouse brain

- Diurnal variation in Aβ levels in brain interstitial fluid and human CSF.
- Sleep deprivation increased amyloid plaque pathology in mice and increases $A\beta_{42}$ in CSF in humans
- **The same holds true for tau!**





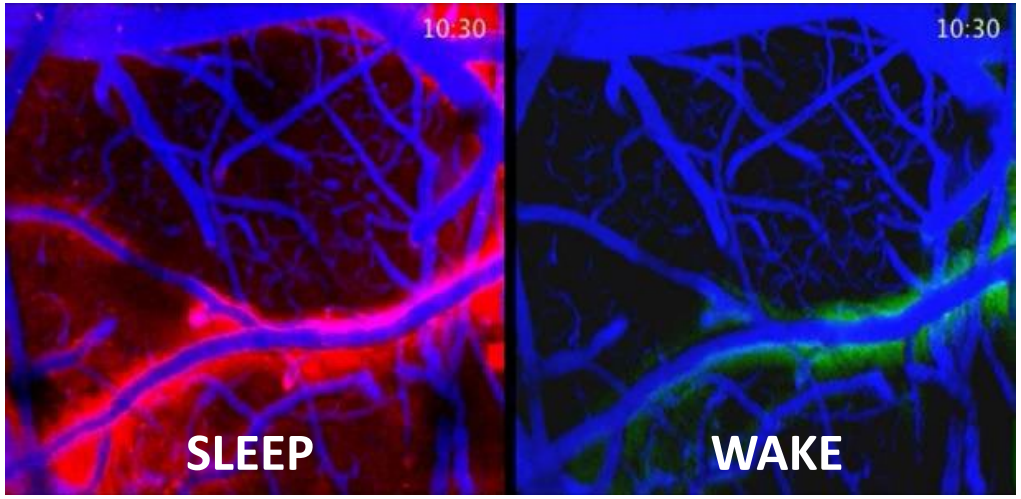


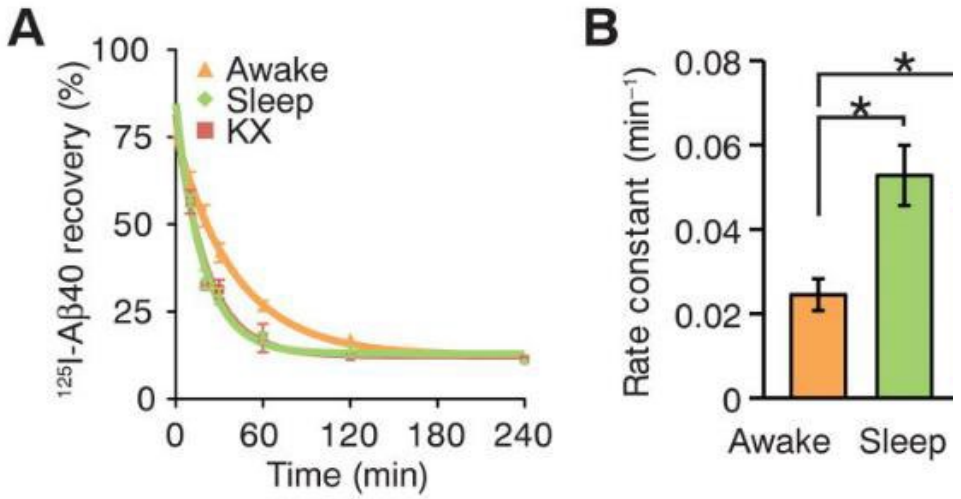


Kang JE et al, *Science,* 2009
Lucey BP et al, *Ann Neurol*, 2018
See also Ooms S et al, *JAMA Neurol*, 2017

Sleep and glymphatic clearance of toxic proteins

- Increased perivascular fluid flow in sleep mice.
  - “Glymphatic system”
- Sleep accelerates clearance of labelled Aβ injected into striatum.
- Early imaging data from human suggests a similar mechanism.
- May also act on tau, α-synuclein

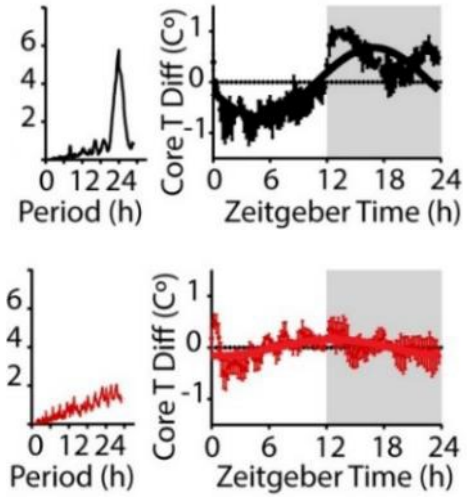


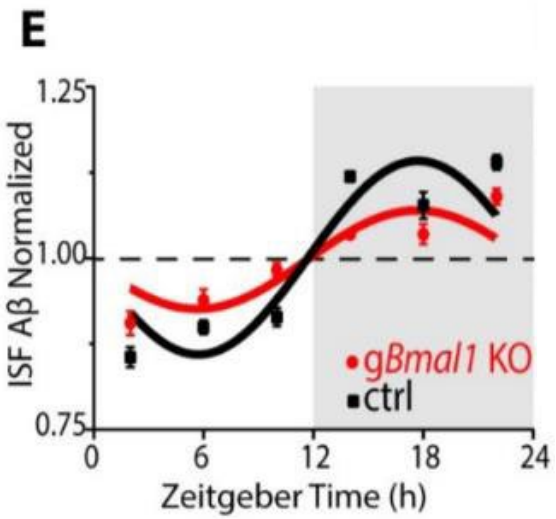


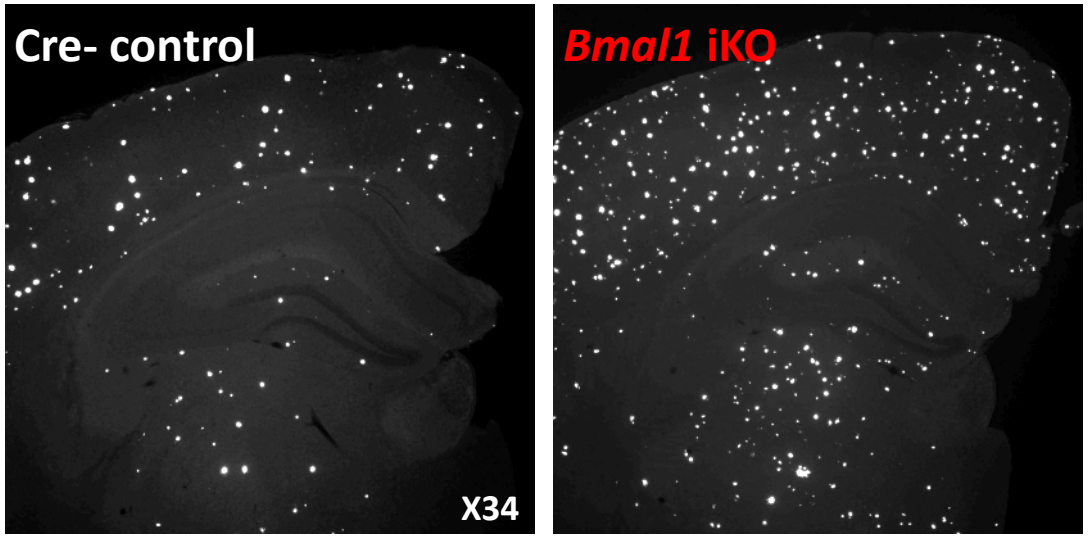
Xie L et al., *Science*, 2013

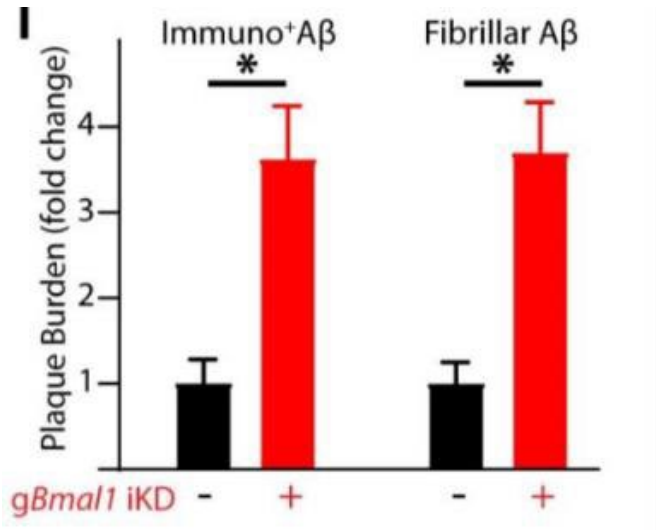
Bmal1 deletion disrupts ISF Aβ rhythms and increases amyloid plaques

- Global deletion of the core clock gene *Bmal1* renders APP/PS1 mice arrhythmic and increased amyloid plaque









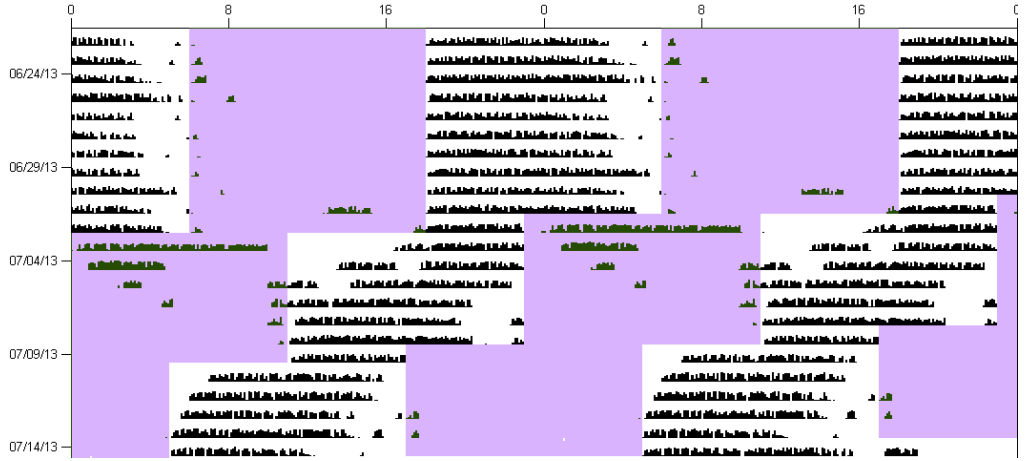
Cre- control

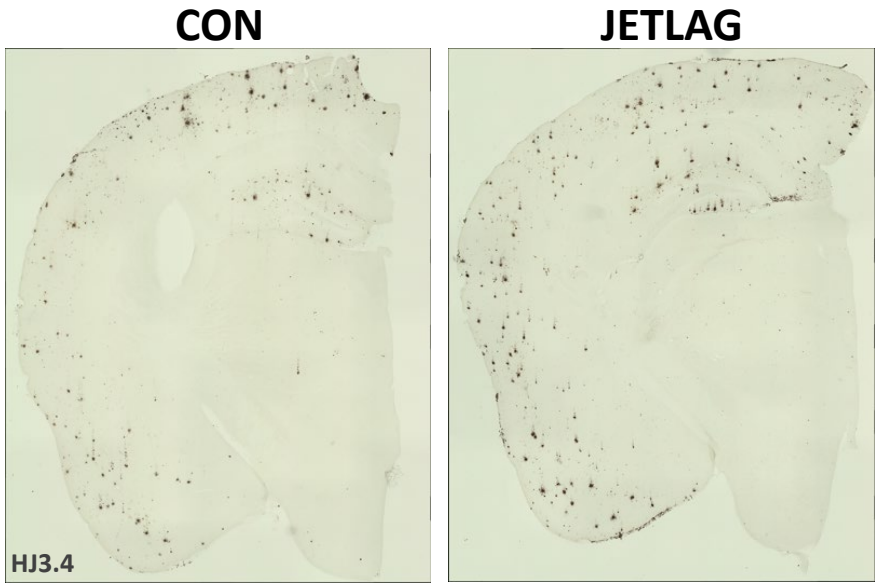
Bmal1 iKO

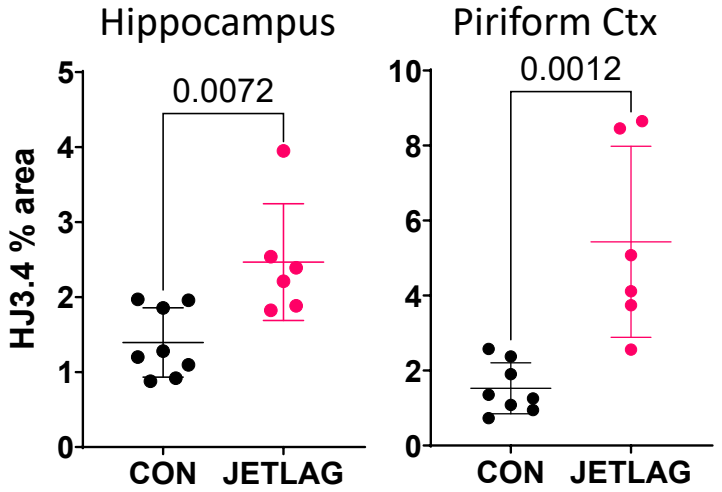
Kress GJ et. al, *J Exp Med,* 2018

Circadian desynchrony increases amyloid plaques

- APP/PS1dE9 mice
- Chronic “jetlag” paradigm
  - 6hr weekly light phase advance (earlier lights-on)
  - Jetlag from 3-6 months of age



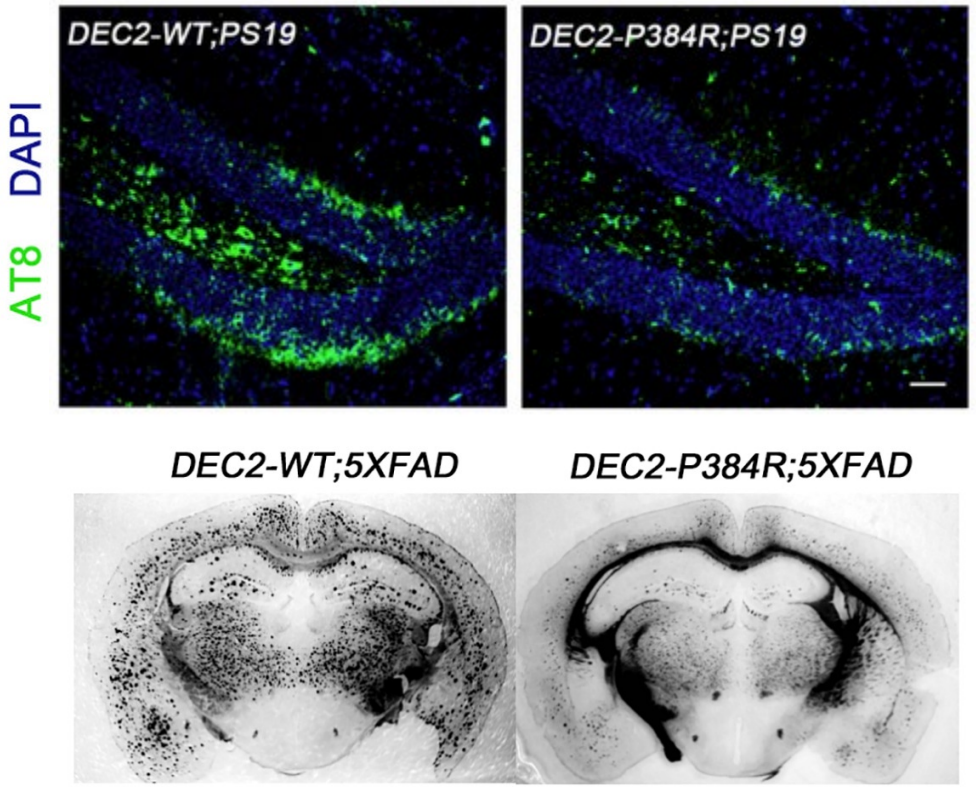




Ashish Sharma, unpublished

Short-sleep mutations reduce AD pathology

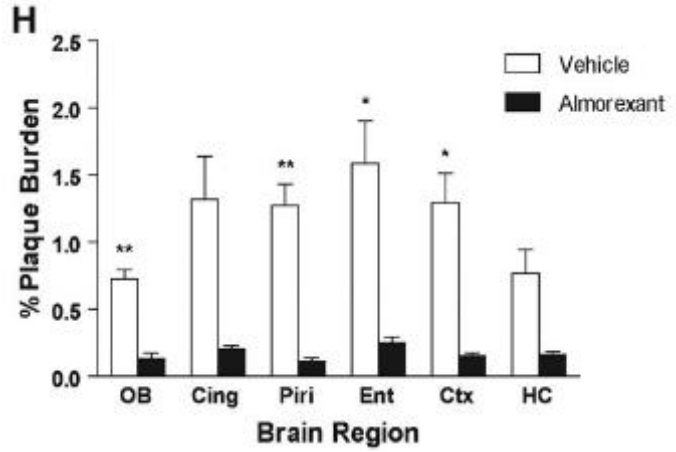
- Short-sleep mutations in humans reduce AD pathology in mice (Fu and Ptacek labs)
- *DEC2* (*BHLHE41*) is a circadian gene- mutation causes short sleep and reduced AD pathology.
- Suggests unique clock-sleep interplay in AD

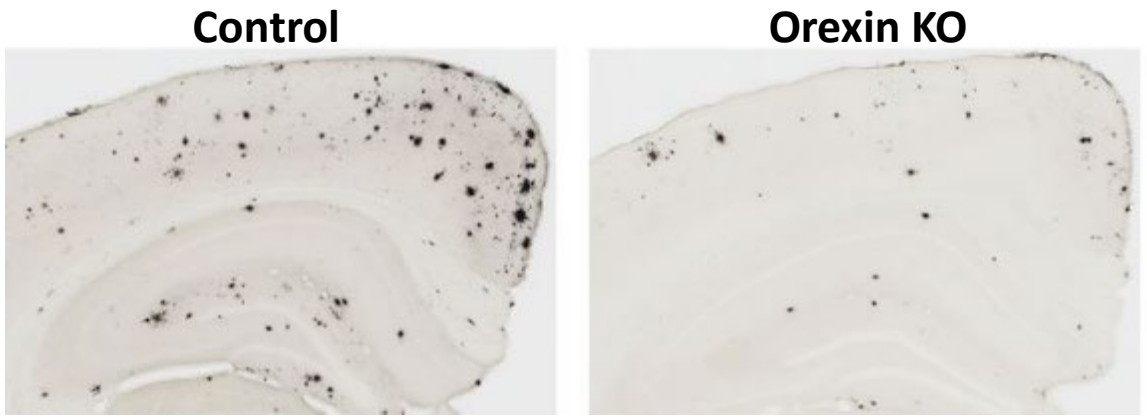


Dong Q et al., *iScience*, 2022

Orexin inhibition mitigates plaque accumulation

- Orexin Antagonists
  - Suvorexant, Lemborexant, daridorexant FDA approved for insomnia
- In mice, blocking orexin function with a drug or deleting the orexin gene increases sleep, *prevents* amyloid plaque formation
- Human AD patients have altered CSF orexin levels
  - See Ligouri C et al, *JAMA Neurol*, 2014; Osorio RS*, Sleep*, 2016.





Kang et al, *Science* 2009; Roh et al, *J Exp Med*, 2014

Future Directions

- Chicken or egg: Does sleep/circadian dysfunction precede preclinical AD pathology, or vice versa?
- What aspect of sleep/circadian dysfunction is most detrimental? Circadian fragmentation? SWS loss? REM loss? OSA? Is there a useful biomarker here?
- Mechanisms: Aβ/tau production vs. clearance? Effects on inflammatory/glial/immune systems?
- Therapies: Sleep drugs as preventative agents for AD? Development of clock-targeted drugs? Targeting downstream pathways ("sleep in a pill").