Sleep and Circadian Rhythms in Neurodegenerative Disorders

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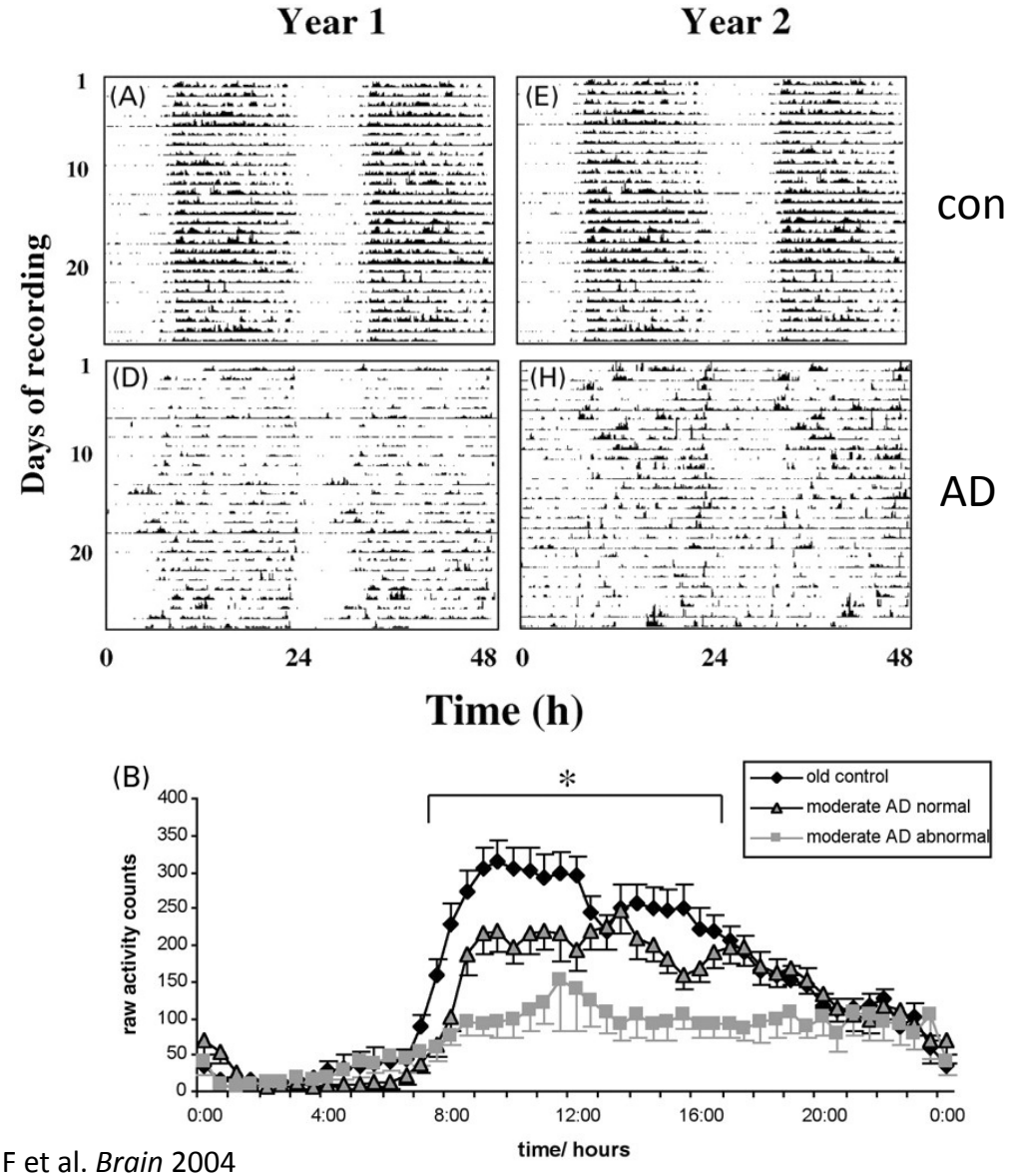
Significance

- Circadian and sleep disturbances are very common in neurodegenerative diseases and are major causes of morbidity and institutionalization
- Altered circadian function may contribute to “sundowning”, another major cause of morbidity in dementia
- Aside from being a symptom of neurodegenerative disorders, sleep and circadian rhythm disorders may contribute to disease pathogenesis.
- Understanding and potentially treating sleep and circadian dysfunction in neurodegenerative diseases could potentially improve quality of life for patients and caregivers, or perhaps alter disease progression

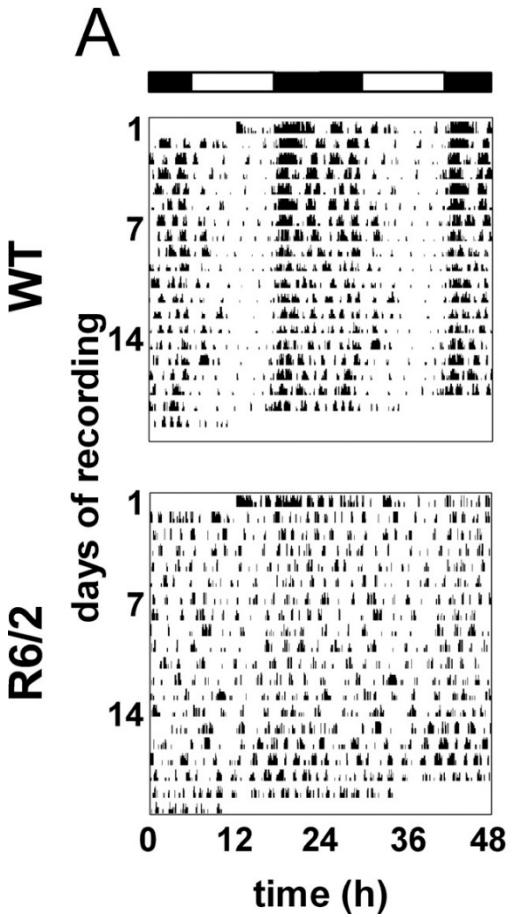
State of the Art Knowledge

- Myriad sleep/circadian changes in neurodegenerative diseases
    - In AD alone, reports of Increased fragmentation, decreased REM and SWS, increased nighttime waking, increased napping, phase advance
- Many of studies demonstrating sleep and circadian disruption in aging and age-related neurodegenerative disease (AD and PD in particular)
- Emerging studies suggesting sleep/circadian alterations may precede dementia
- Manipulating sleep and the circadian clock has direct impact on neurodegenerative process in mice

Circadian dysfunction is common in neurodegenerative diseases



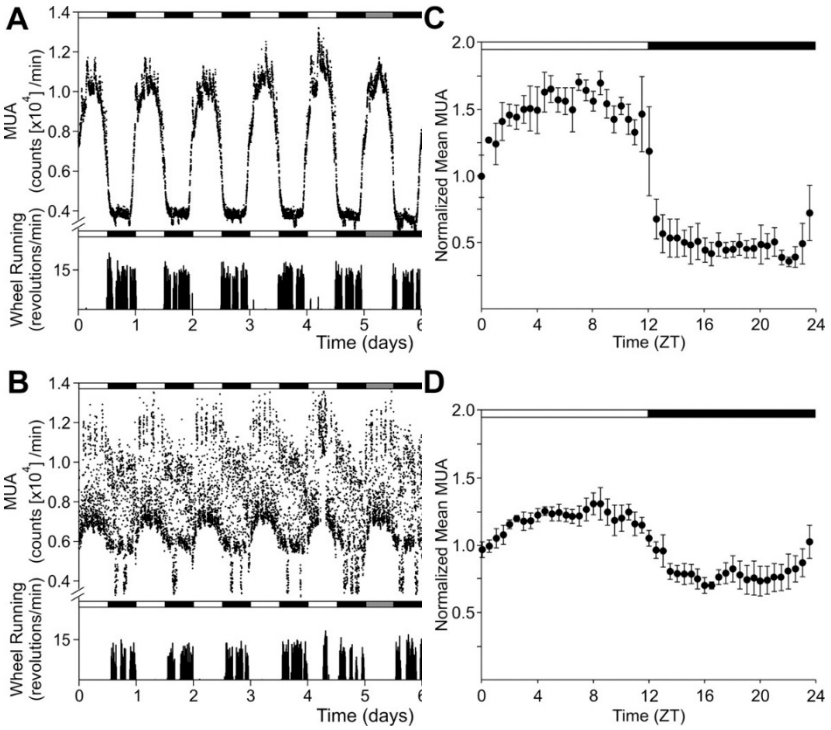
Hatfield C F et al. *Brain* 2004



Pallier P N et al. *J. Neurosci.* 2007

Circadian output declines in aging and AD

Mouse SCN



-Loss of pineal gland clock gene oscillation and melatonin rhythms in AD

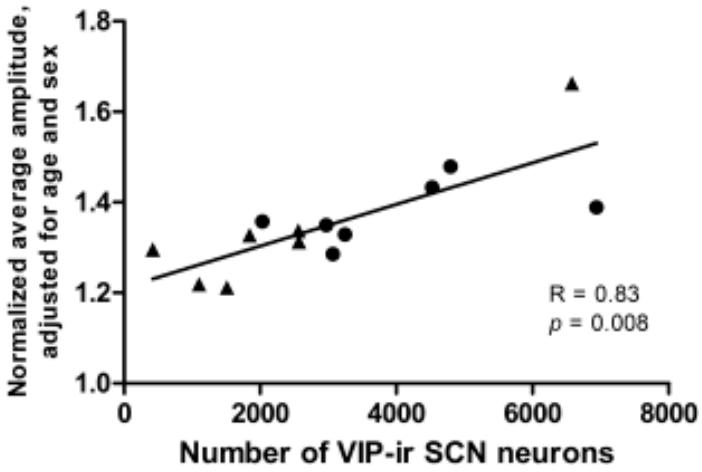
-Circadian abnormalities in several strains of APP and PS1/APP transgenic mice

Nakamura T J et al. *J. Neurosci.* 2011

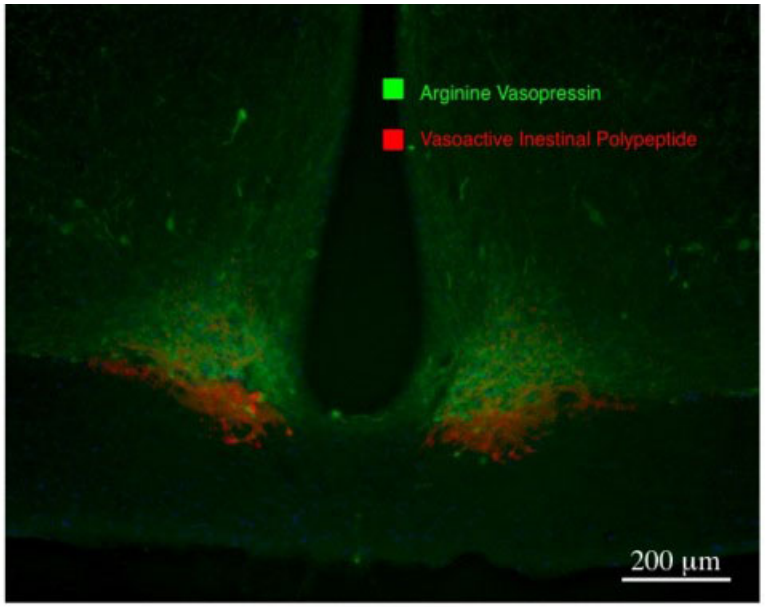
Wu wt al, FASEB, 2006

SCN pathology in aging and AD

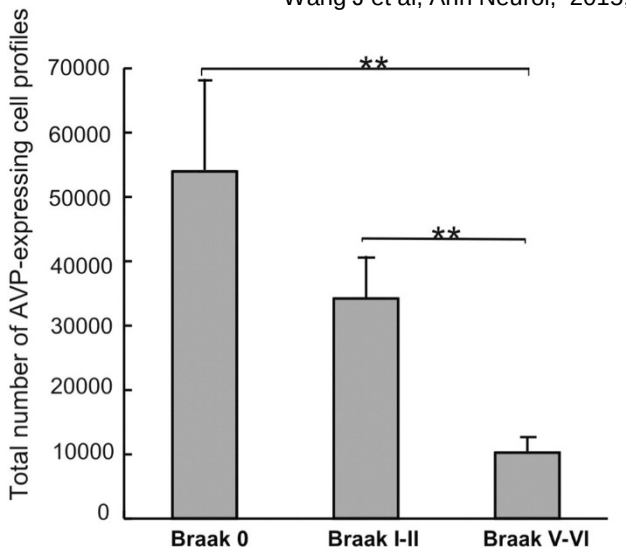
- Loss of AVP- and VIP-expressing neurons in SCN in aging and AD
- Tangles but no plaques in SCN



Wang J et al, Ann Neurol, 2015, 78; 317-22



Paul & Schwartz



Ying-Hui Wu et al. FASEB J 2006;20:1874-1876

Sleep and circadian alterations may precede dementia I

Circadian Activity Rhythms and Risk of Incident Dementia and Mild Cognitive Impairment in Older Women

Gregory J. Tranah, PhD,[1] Terri Blackwell, MA,[1] Katie L. Stone, PhD,[1]
Sonia Ancoli-Israel, PhD,[2] Misti L. Paudel, MPH,[3] Kristine E. Ensrud, MD,[3,4,5]
Jane A. Cauley, DrPH,[6] Susan Redline, MD,[7] Teresa A. Hillier, MD,[8]
Steven R. Cummings, MD,[1] and Kristine Yaffe, MD[9,10,11] for the SOF Research Group

ANN NEUROL 2011;70:722–732

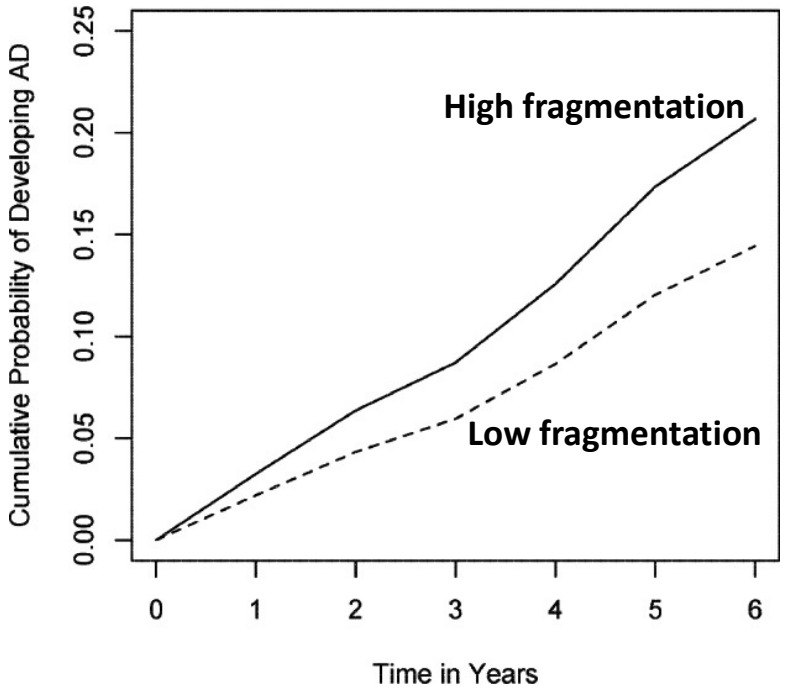
"Older, healthy women with decreased circadian activity rhythm amplitude and robustness, and delayed rhythms have increased odds of developing dementia"

SLEEP FRAGMENTATION AND RISK OF ALZHEIMER DISEASE AND COGNITIVE DECLINE

http://dx.doi.org/

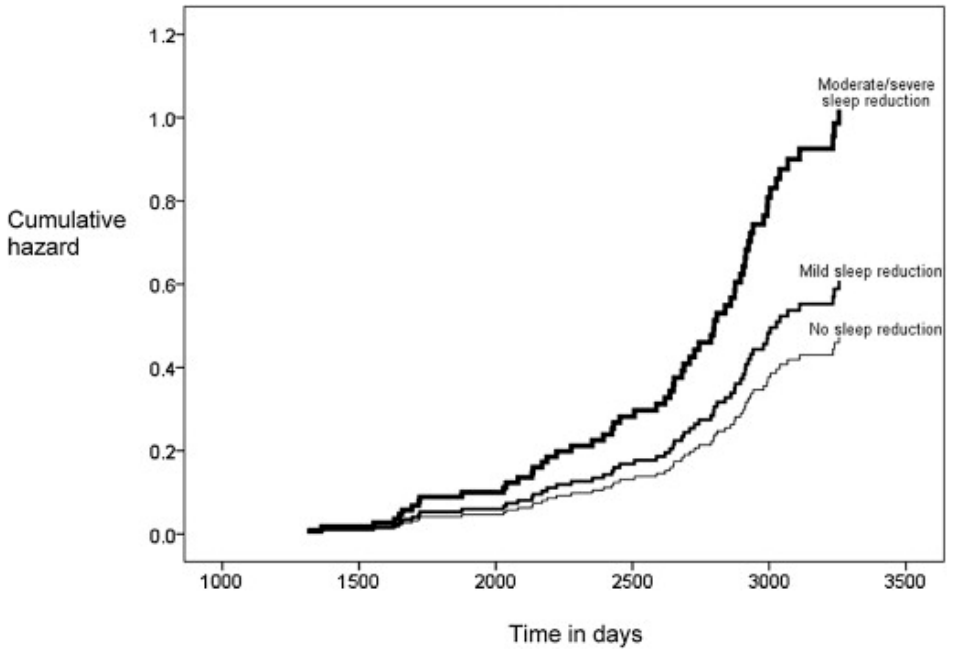
Sleep Fragmentation and the Risk of Incident Alzheimer's Disease and Cognitive Decline in Older Persons

Andrew S. P. Lim, MD[1]; Matthew Kowgier, PhD[2]; Lei Yu, PhD[3,4]; Aron S. Buchman, MD[3,4]; David A. Bennett, MD[3,4]



Sleep and circadian alterations may precede dementia II

- Self-reported sleep problems increase risk of subsequent dementia (1yr)
- Cognitively-normal people with biomarkers of Aβ pathology have slightly decreased sleep efficiency



Hahn et al, Am J Ger Psych, Vol22,, 2014, 1262–1271

Table 2. Sleep Measures and Nap Characteristics

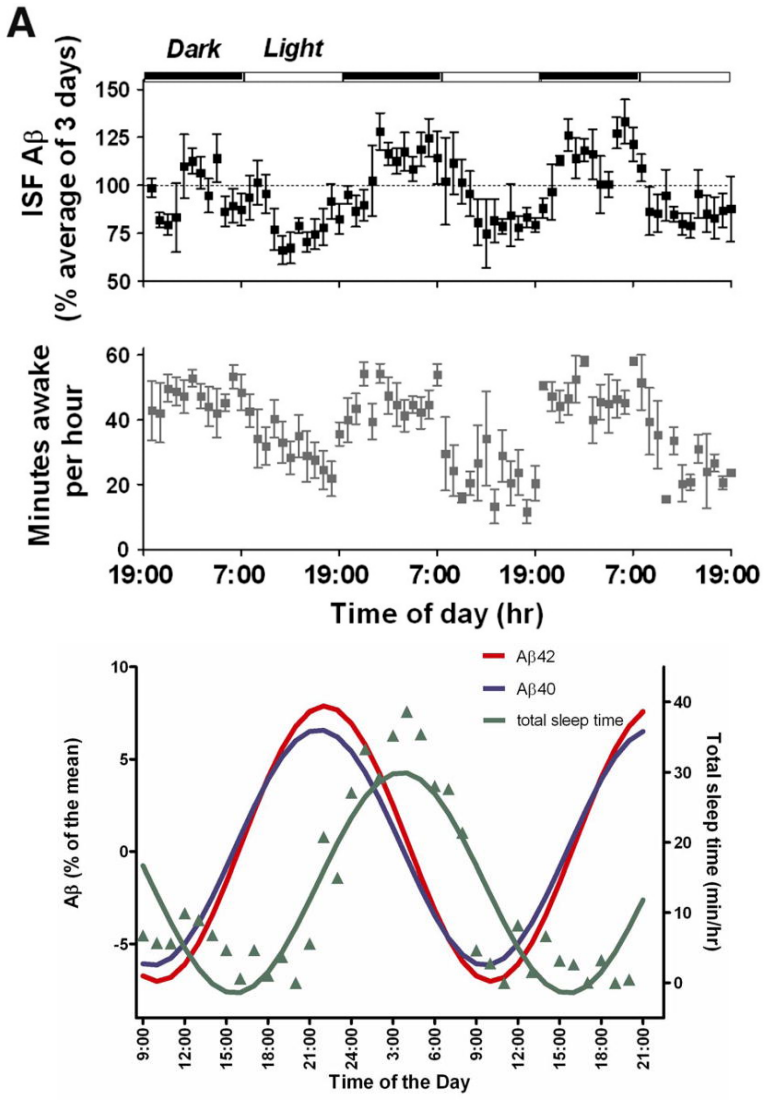
Variable	Mean (SD) All (n = 142)	Aβ42 Level >500 pg/mL (n = 110)	Aβ42 Level ≤500 pg/mL (n = 32)	95% CI of Group Differences
Sleep efficiency, %	82.9 (6.2)	83.7 (5.6)	80.4 (7.7)	0.8 to 5.7
Wake time after sleep onset, min	56.1 (22.6)	54.0 (21.8)	63.1 (23.9)	−17.9 to −0.21
Total sleep time, min	402.6 (44.6)	403.0 (47.3)	401.3 (49.0)	−16.0 to 19.5
Time in bed, min	486.4 (49.8)	482.3 (47.3)	500.6 (55.8)	−37.9 to 1.23
Nap days per week[a]	1.4 (1.7)	1.3 (1.6)	1.9 (1.9)	−1.3 to 0.1
Frequent naps (≥3 d per week), No. (%)	26 (18.4)[a]	16 (14.7)[a]	10 (31.2)	−0.32 to −0.01

Abbreviation: Aβ42, β-amyloid 42.
[a]One participant was missing sleep diary nap data.

Ju et al, JAMA Neurol. 2013;70(5):587-59

Amyloid-β levels shows circadian oscillation in brain ISF

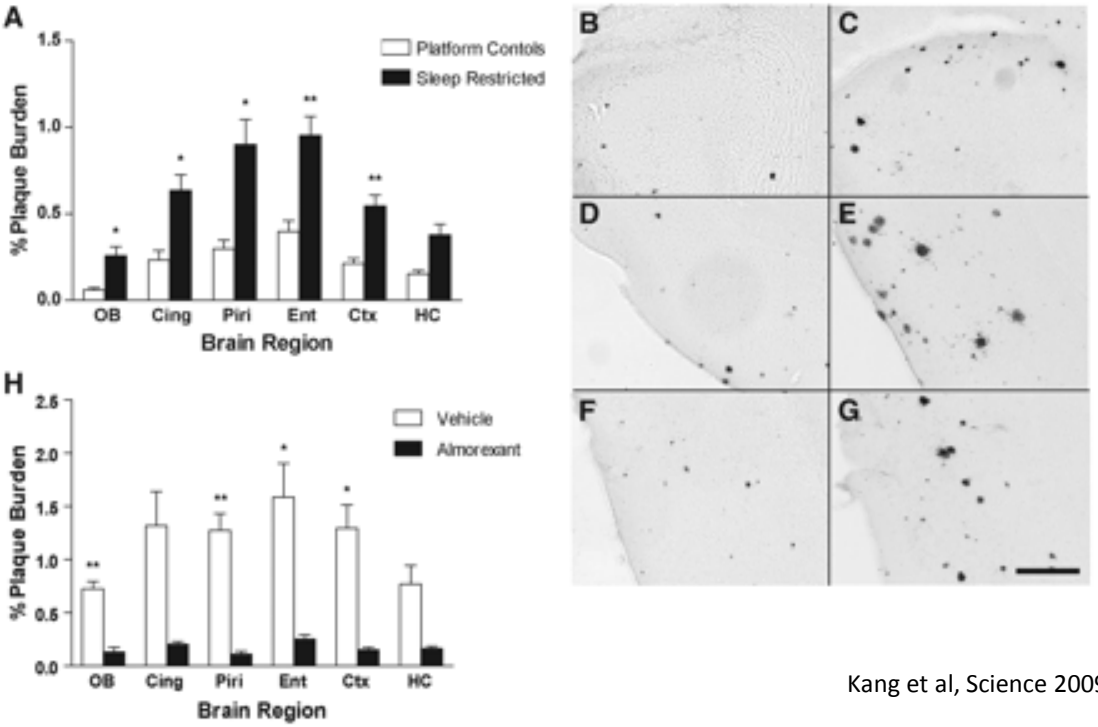
- Diurnal variation in Aβ levels in ISF by microdialysis
- Aβ increases during dark (waking) and decreases during light (sleep)
- Aβ in human CSF shows a similar oscillatory pattern
- Is this controlled by the clock?



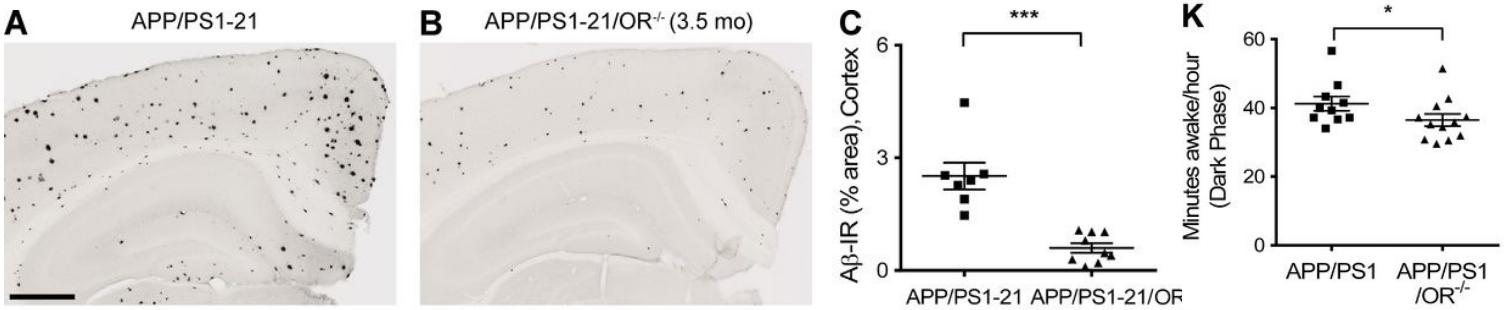
Kang et al, *Science* 2009; Huang et al, Arch Neurol, 2012

Manipulating sleep-wake impacts Aβ pathology in mice

- Sleep deprivation increases, while orexin antagonists or orexin gene deletion decreases Aβ plaque burden in PS1/APP mice.

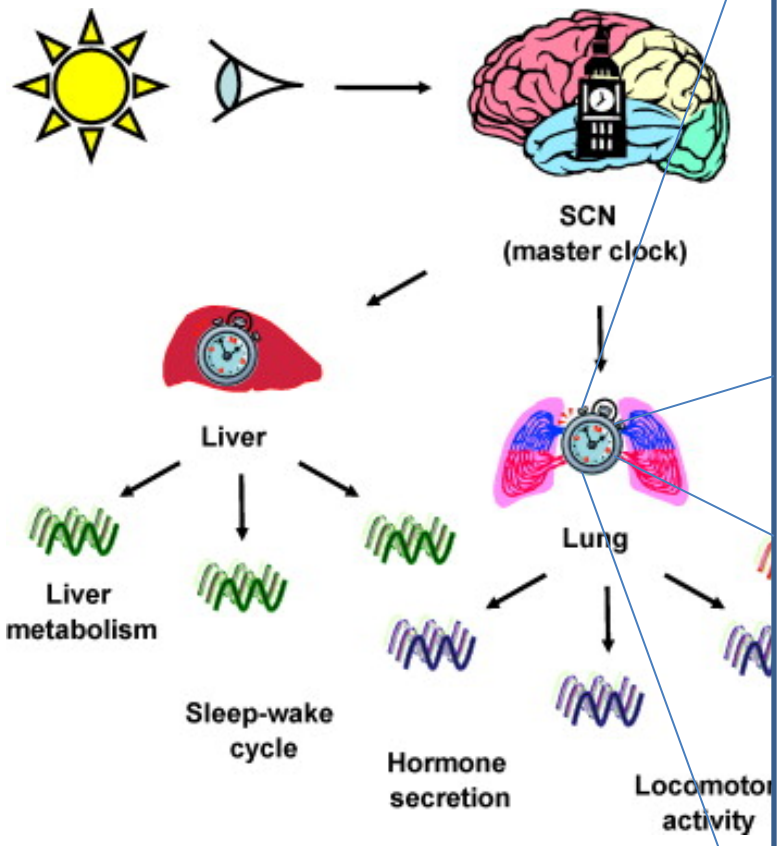


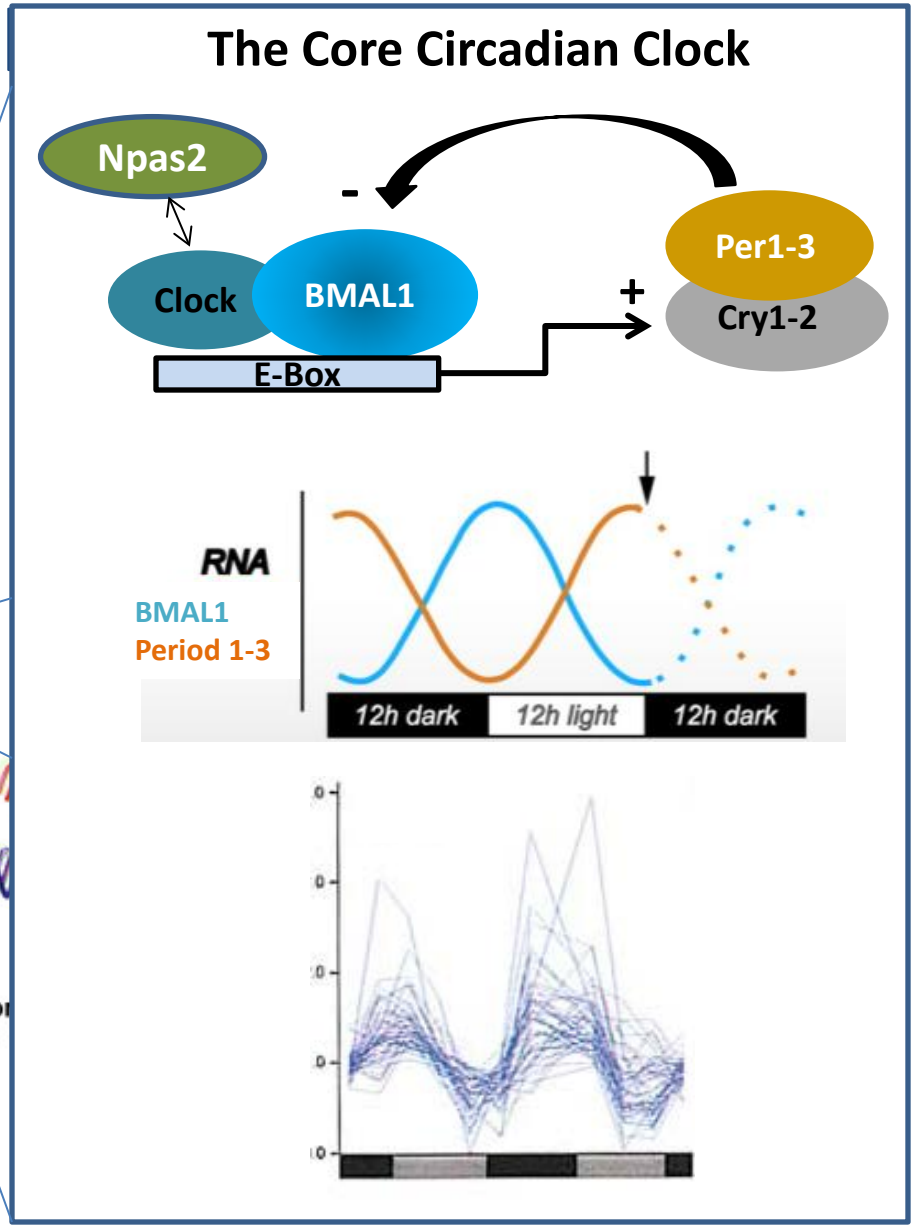
Kang et al, Science 2009



Roh et al. J Exp Med 2014;211:2487-2496

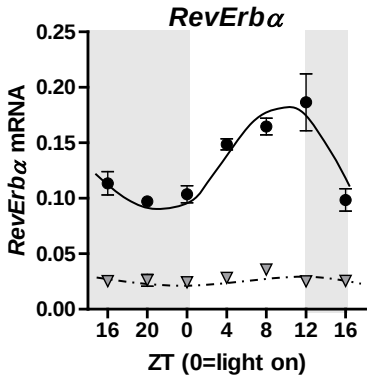
The canonical

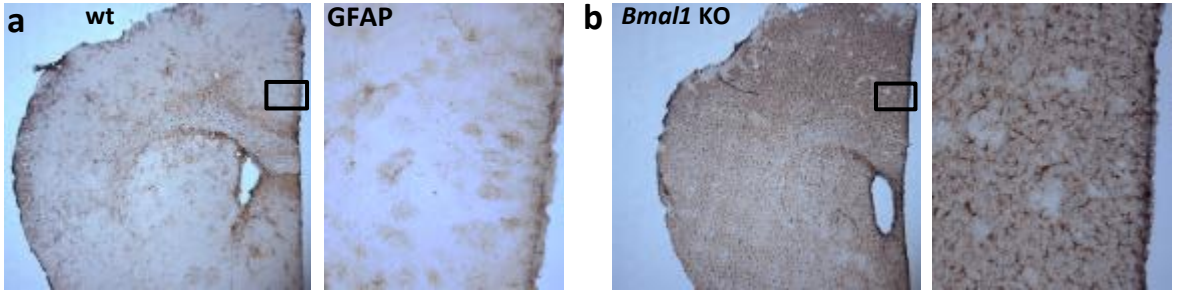


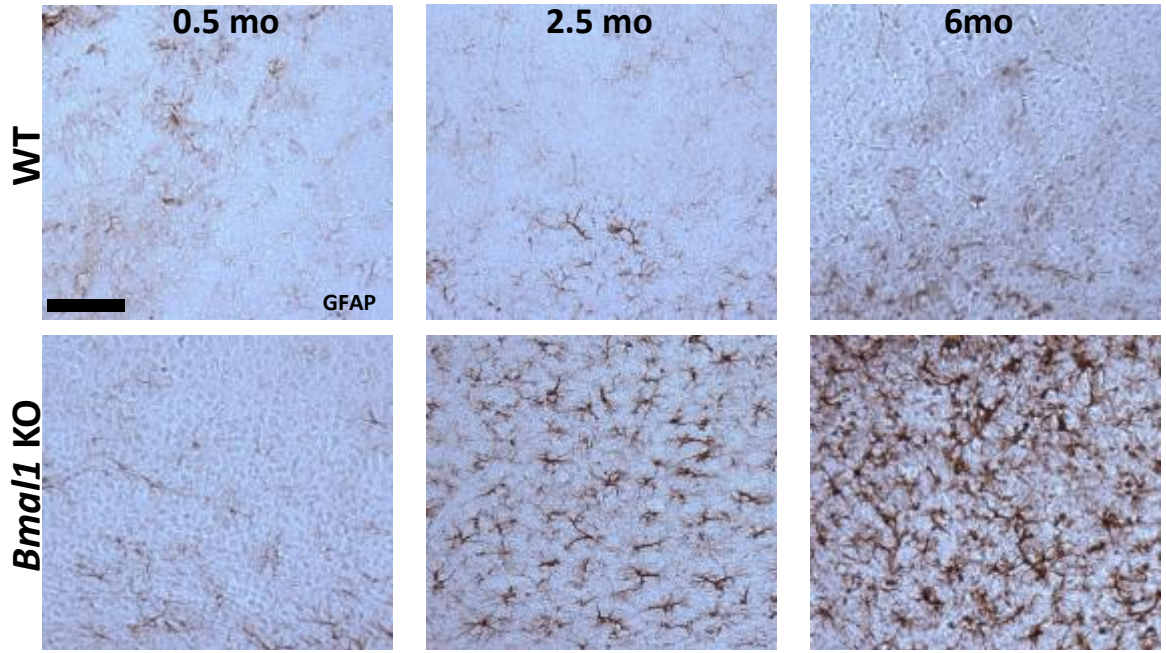


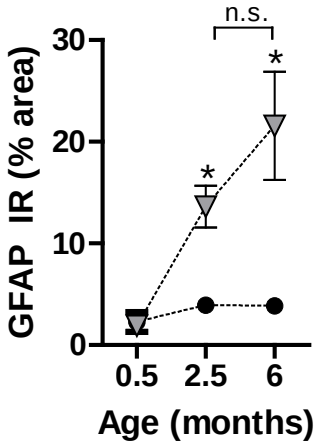
Kondratov R, Aging Res Rev, 2007

Bmal1 deletion causes astrogliosis throughout the brain





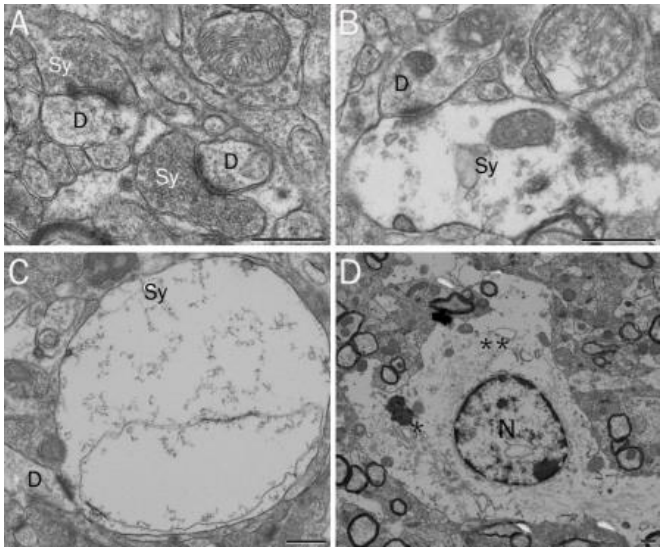




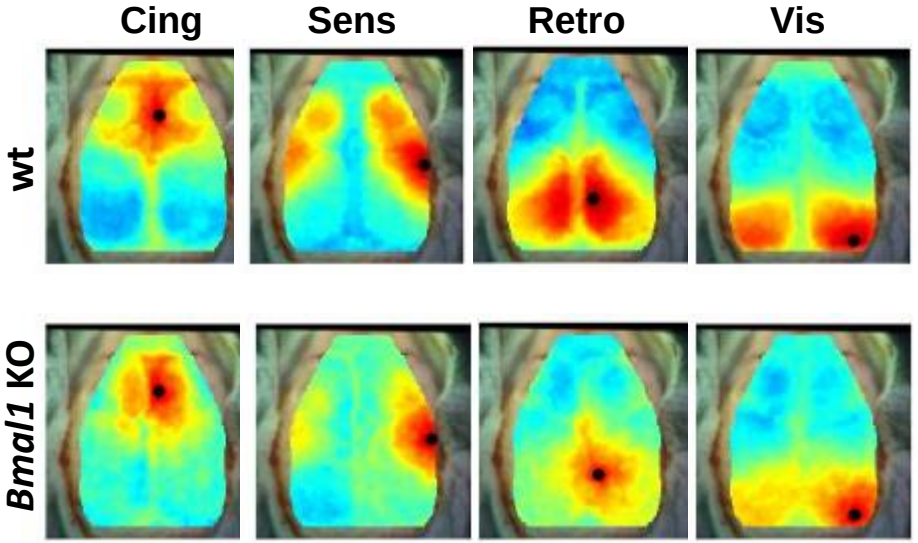
Musiek et al., *J Clin Invest*, 2013

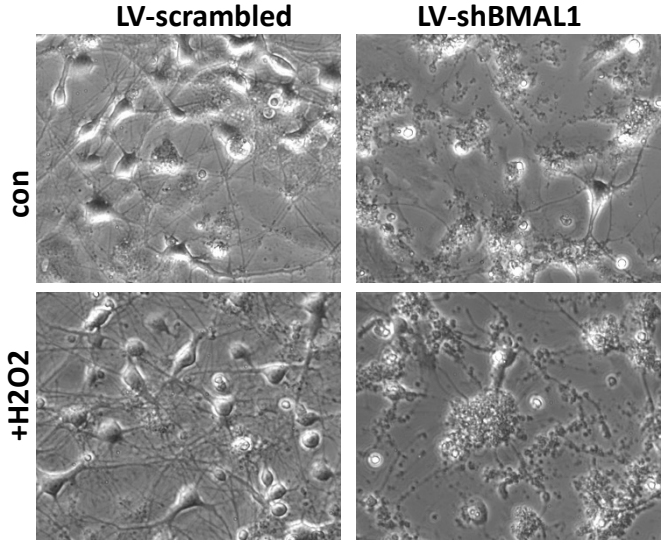
Neuronal injury and oxidative stress in *Bmal1* KO cortex

Synaptic degeneration

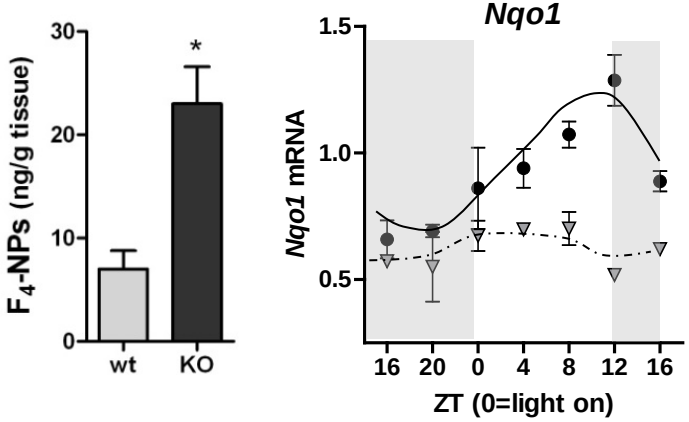


Impaired functional connectivity





Oxidative stress



Gaps in Knowledge

- What is the role of sleep/circadian dysfunction in early/presymptomatic-stages of neurodegenerative diseases?
- Is the root cause degeneration of circadian systems (SCN, peripheral oscillators) or sleep circuitry?
    - What happens to core clock function?
- What pathogenic mechanisms cause degeneration of sleep and circadian nuclei?
- Can a broken clock be fixed? Behaviorally (light, melatonin) or pharmacologically?
- Are sleep or circadian systems legitimate therapeutic targets to prevent or forestall neurodegenerative diseases?

Research Opportunities

- Clinical/Translational:
  - Characterizing sleep and circadian abnormalities in early AD or PD in relationship to other biomarkers of disease
  - Going beyond actigraphy- developing new methods for monitoring sleep/circadian function in human populations
  - Intervention studies: impact of sleep deprivation or orexin antagonists on cognition, pathologic endpoints

Research Opportunities

- Basic:
  - Develop animal model of sundowning: what is the cellular/molecular basis?
  - Molecular mechanisms connecting sleep disruption to Aβ pathology
  - Dissecting the impact of sleep/circadian dysregulation on other neurodegenerative pathways and neural function in general
  - Many, many other directions!

Questions?