Sleep, Aging, and Brain Health: Implications for Prevention

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Major Demographic Shift

- The U.S. population is aging
- The “oldest old” are the fastest-growing segment of our population
- This will have significant implications for the prevalence of dementia, particularly Alzheimer’s disease (AD)

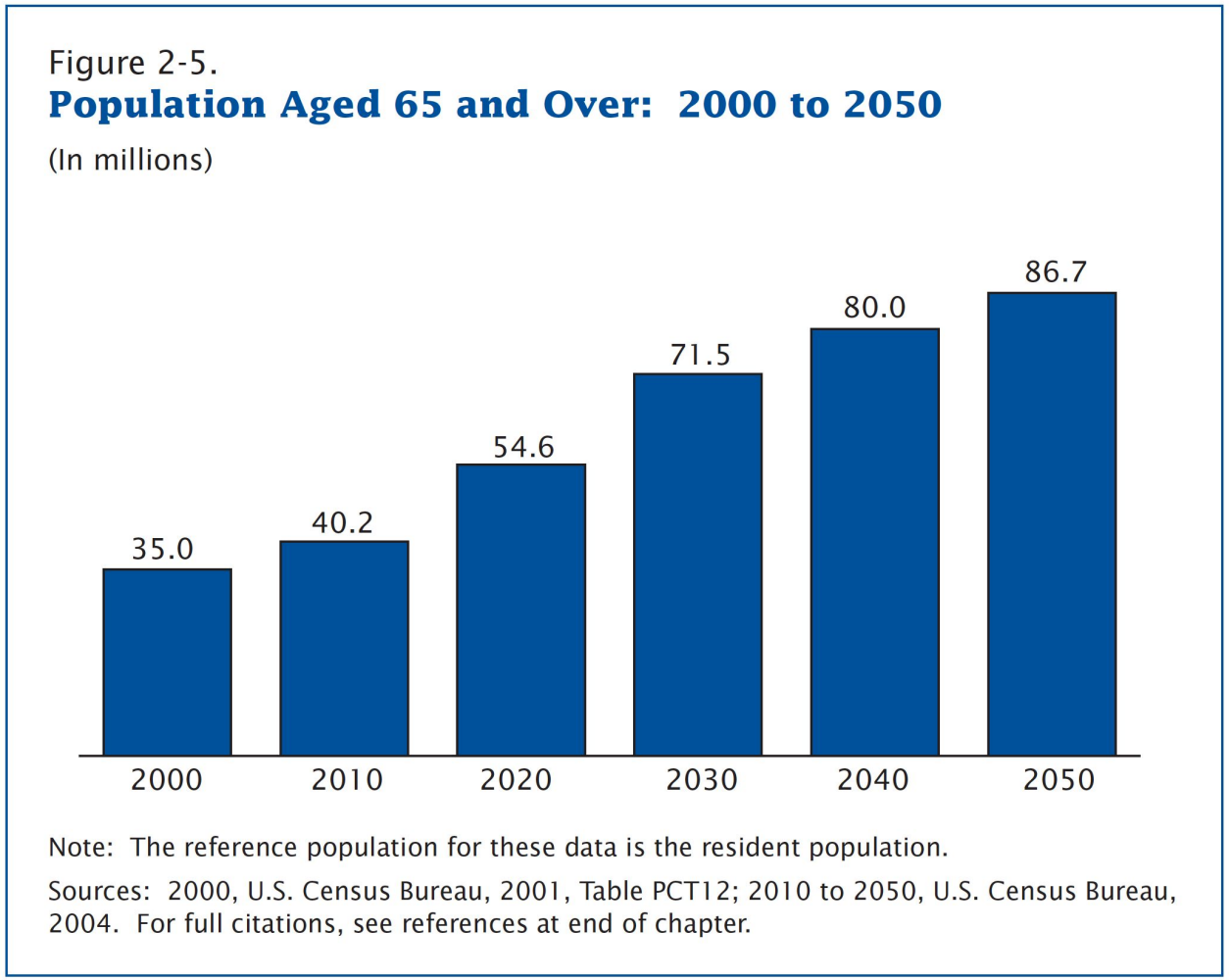


Figure 2-5: He et al., U.S. Census Bureau; 2005.

What does this have to do with sleep?

- Sleep disturbances are common in older adults
- Growing evidence suggests that poor sleep is associated with cognitive decline, AD, and dementia
- There is no cure or effective treatment for AD, so prevention is critical
- Late-life sleep disturbance often is treatable
- Modifiable risk factor for AD and other dementias?

Prevalence of Sleep Complaints in Older Adults

- ~9,300 community-dwelling older adults, from 3 communities
- Mean age = 74
- >80% complaint “sometimes” or “most of the time”

% of sample reporting having a complaint “most of the time.”					
Trouble falling asleep	Waking up during night	Waking up too early	Need nap during day	Awakes not rested	Any chronic complaint
19	30	19	25	13	57

Foley et al. *SLEEP,* 1995.

Why are sleep complaints so common in later life?

- Normal age-related changes in sleep
- Medical & psychiatric disorders
- Medications
- Decreased physical function
- Psychosocial changes
- Changes in circadian rhythms
- Sleep disorders (e.g., sleep-disordered breathing)

Ancoli-Israel & Cooke, *J Am Geriatr Soc*, 2005; Vaz Fragoso & Gill, *J Am Geriatr Soc,* 2007. Czeisler et al., *Lancet*, 1992; Weitzman, *Neurobio of Aging*, 1982; Young et al., *Am J Respir Crit Care Med,* 2002; Ancoli-Israel et al., *SLEEP,* 1991.

Sleep in Alzheimer's Disease

- Shorter, more fragmented sleep
- Lower sleep efficiency
- Reduced slow-wave sleep and REM sleep
- Greater dementia severity is associated with greater sleep fragmentation

Feinberg et al., *J Psychiatr Res,* 1967; Moe et al., *J Sleep Res,* 1995; Prinz et al., *J Am Geriatr Soc,* 1982; Prinz et al., *Neurobiol Aging,* 1982; Vitiello et al., *J Gerontol.,* 1990; Mortimer et al., *Neurology,* 1992

Reasons for Disturbed Sleep in Alzheimer's Disease

- Loss of brain volume
  - Suprachiasmatic nucleus
  - Intermediate nucleus
- Alterations in cholinergic system
- Reduced exposure to bright light
- Reduced daytime activity + more napping

Swaab et al., *Brain Research,* 1985; Lim et al., *Brain,* 2014; Campbell et al., *Physiology & Beh,* 1988; Montplaisir et al., *SLEEP,* 1995; Platt & Riedel, *Beh Brain Res,* 2011.

Self-Reported Sleep and Cognition

- Poorer sleep quality: lower global cognitive performance & executive function
- Difficulty falling or staying asleep: lower performance and decline on global cognitive measures
- Poorer attention & executive function in insomnia
- Conflicting results re: sleep duration & cognition

Nebes et al., *J of Ger Psy Sci,* 2009; Tworoger et al., *Alz Dis Assoc Disord, 2006;* Cricco et al., *J Am Ger Soc*, 2001; Jelicic et al., *Int J Ger Psy* 2002; Vignola et al., *J Geron Psy Sci,* 2000; Haimov et al., *Behav Sleep Med*, 2008; Hart et al., *Aging Cognit*, 1995; Benito-León et al., *J Psychiatr Res*, 2013.

Sleep Fragmentation and Incident AD

- *N* = 737 adults from Rush Memory and Aging Project (mean age = 81.6 ±7.2), without dementia at baseline
- 10 days of actigraphy
- Sleep fragmentation measured by k_{RA} index
- Incident AD defined on basis of 19 cognitive tests, NINDS-ADRDA criteria
- 3.3 years of follow-up

Lim et al. *SLEEP,* 2013;36:1027-32.

Lim et al., 2013

- Risk of incident AD (per SD) HR = 1.22 (95% CI 1.03, 1.44)
- Those in 90th %ile had 1.5 times the risk of incident AD compared to those in 10th %ile

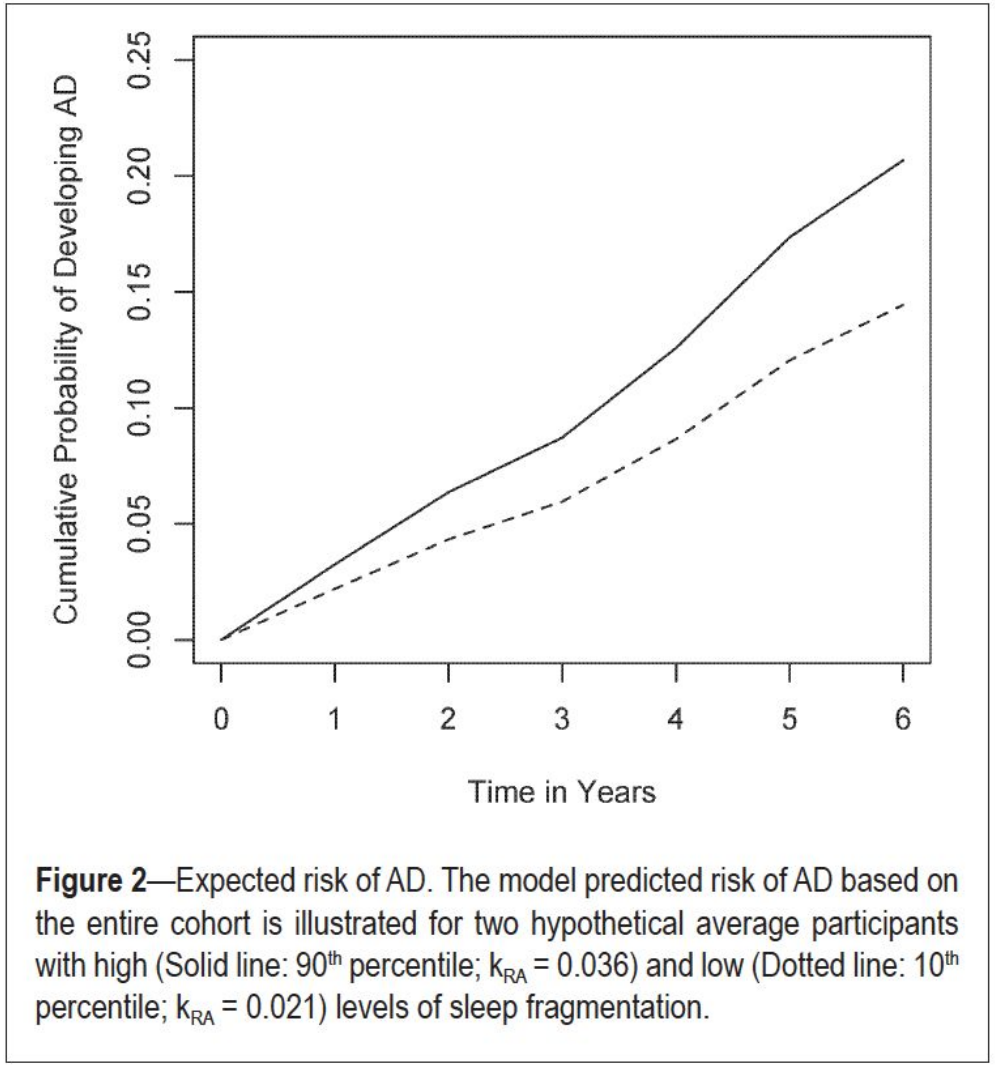
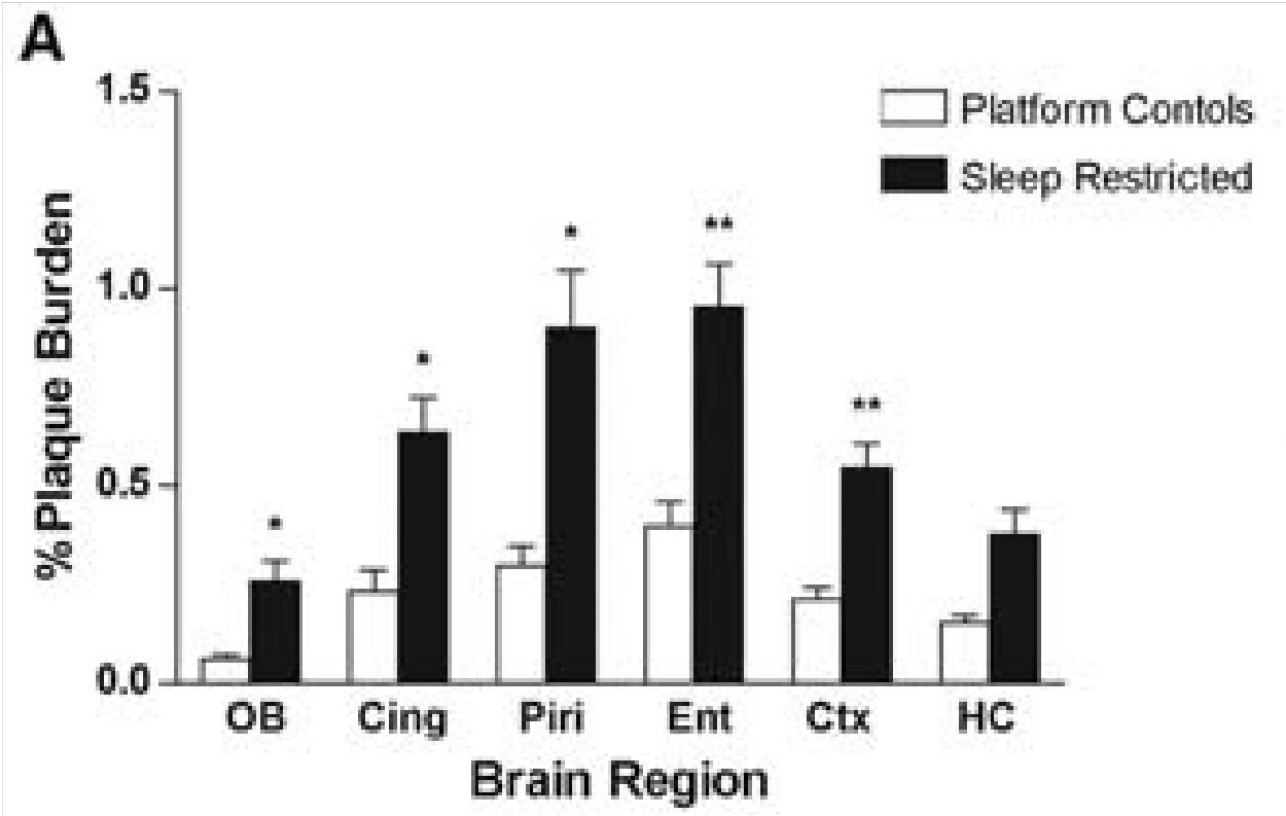


Figure 2—Expected risk of AD. The model predicted risk of AD based on the entire cohort is illustrated for two hypothetical average participants with high (Solid line: 90th percentile; k_{RA} = 0.036) and low (Dotted line: 10th percentile; k_{RA} = 0.021) levels of sleep fragmentation.

Lim et al. *SLEEP,* 2013;36:1027-32. (p. 1030)

Seminal Study: Kang et al. (2009)

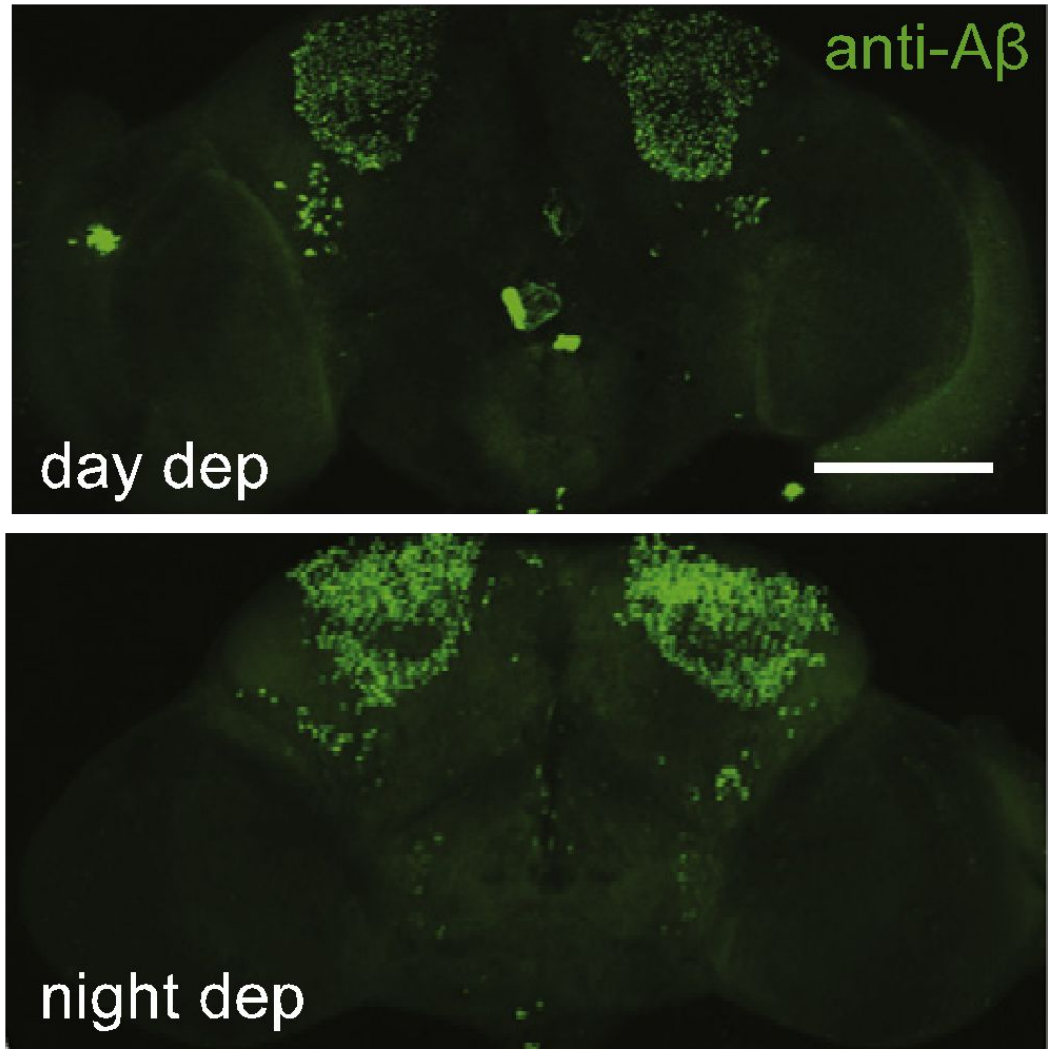
- In AD mouse model, Aβ peptide in brain ISF decrease during sleep, increase during wake
- Similar changes occur in younger humans
- Sleep restriction promotes β-amyloid deposition in the AD mouse



Kang et al., *Science* 2009;326:1005-7.

Sleep loss and AD in Fruit Flies

- Recent research from Dr. Mark Wu's lab
- *Drosophila melanogaster* model of Alzheimer's disease
- Sleep deprivation (~1 hr sleep at night) increases amyloid deposition



Tabuchi et al., *Current Biology* 2015;25:702-712.

Self-Reported Sleep and Amyloid Deposition

- 70 adults from Baltimore Longitudinal Study of Aging
- mean age = 76 (53-91)
- 47% women, 19% African American
- 16.8 ±2.3 years of education
- Self-reported sleep variables
- [^{11}C]PiB PET scan within 5 years of reporting sleep variables

Spira et al., 2013. *JAMA Neurology,* 70(12); 1537-1543

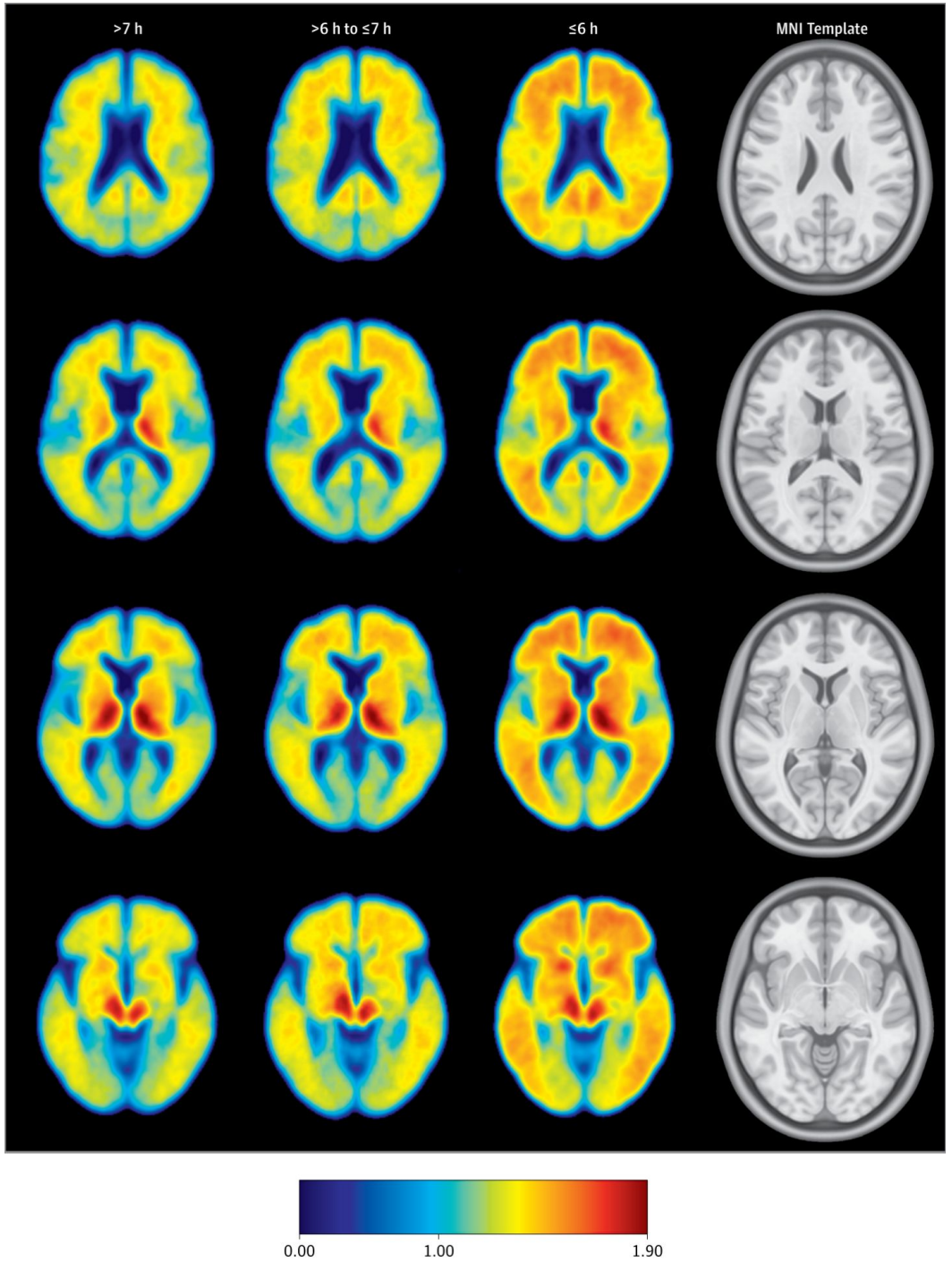
Association of self-reported sleep with amyloid burden.

	B (95% CI)	*p*
Shorter sleep duration		
Cortical DVR	**0.08 (0.03, 0.14)**	**0.005**
Precuneus DVR	**0.11 (0.03, 0.18)**	**0.007**
Trouble falling asleep		
Cortical DVR	0.03 (-0.003, 0.07)	0.071
Precuneus DVR	0.05 (-0.005, 0.10)	0.076
Wake several times		
Cortical DVR	0.01 (-0.02, 0.04)	0.715
Precuneus DVR	0.01 (-0.03, 0.05)	0.690
Worse sleep quality		
Cortical DVR	0.04 (-0.01, 0.09)	0.130
Precuneus DVR	**0.08 (0.01, 0.15)**	**0.025**

N = 70 for all analyses except sleep duration (*N* = 62). Adjusted for age, sex, race, CES-D, BMI, APOE e4 status, cardiovascular or pulmonary disease, use of sleep medication

Spira et al. 2013. *JAMA Neurology,* 70(12); 1537-1543

Unadjusted mean PiB images showing greater Aβ burden with shorter sleep duration (*N* = 62).



Spira et al. 2013. *JAMA Neurology,* 70(12); 1537-1543.

Sleep Duration and Gray Matter Atrophy

- 122 participants in BLSA Neuroimaging Study
- 66.6 ±8.0 years at sleep assessment; 69.5 ±7.6 years at first MRI
- Baseline self-reported average sleep duration; we categorized as <7 hours, 7 hours, or >7 hours
- Mean of 7.6 1.5-T MRI scans (range 3-11) over 8.0 years (range 2.0-11.8)
- Gray matter atrophy: repeated measures of cortical thickness
- We only used data from visits at which participants were cognitively normal.

Spira et al., *SLEEP,* 2016;39:1121-8.

<7 hrs. vs. 7 hrs. (ref)

Region	Hemisphere	Surface Area (mm^2)	Peak F-Statistic
Superior temporal sulcus	LH	330.90	-20.11
Superior temporal gyrus	LH	558.98	-12.10
Inferior frontal gyrus	LH	385.01	-16.98
Middle frontal gyrus	LH	240.37	-15.51
Superior frontal sulcus	LH	621.57	-12.39
Superior frontal gyrus	RH	464.49	-13.54

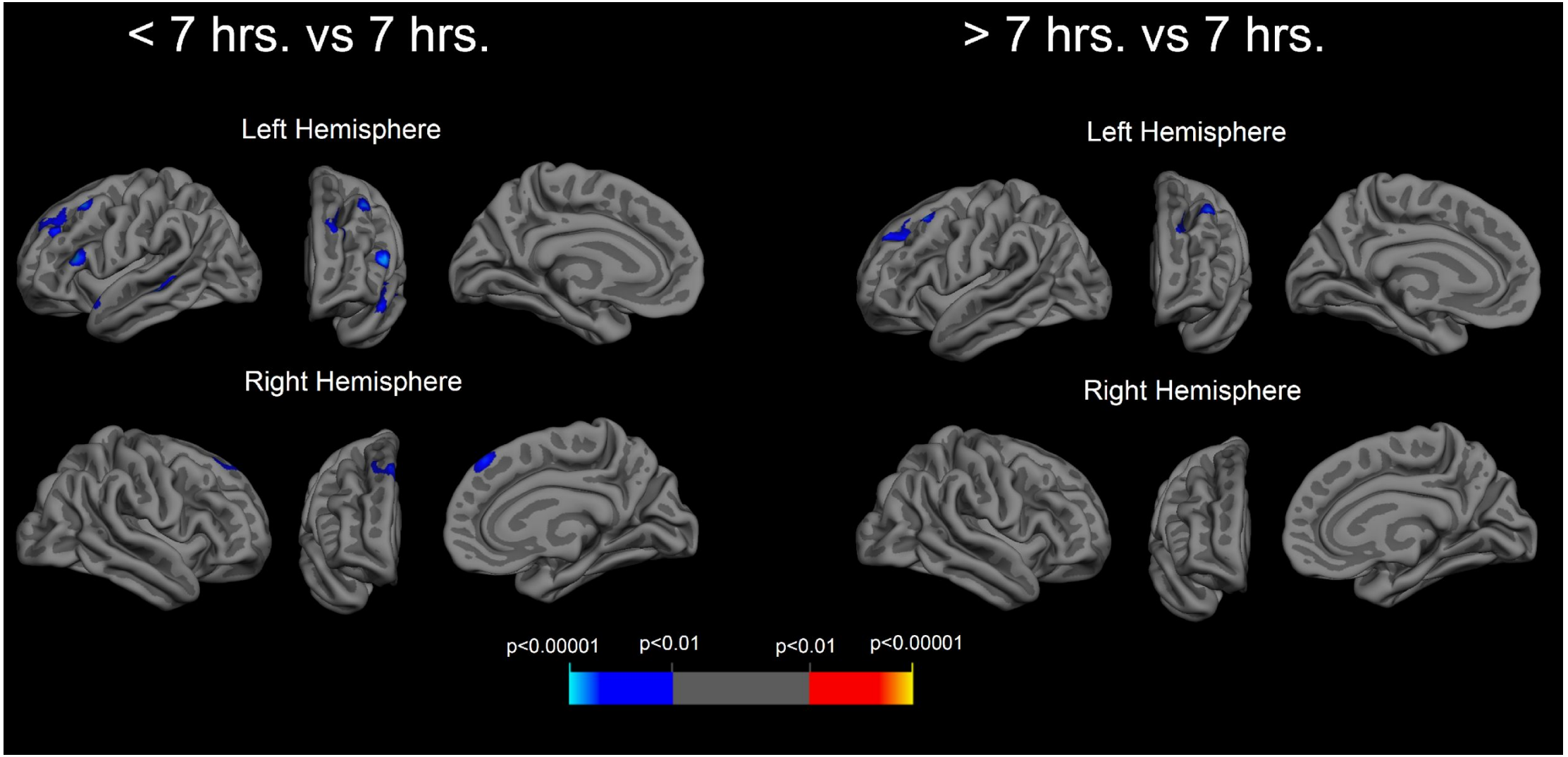
Spira et al., *SLEEP,* 2016;39:1121-8.

>7 hrs vs. 7 hrs (ref)

Region	Hemisphere	Surface Area (mm^2)	Peak F-Statistic
Superior frontal gyrus	LH	355.04	-11.80
Middle frontal gyrus	LH	265.12	-15.10

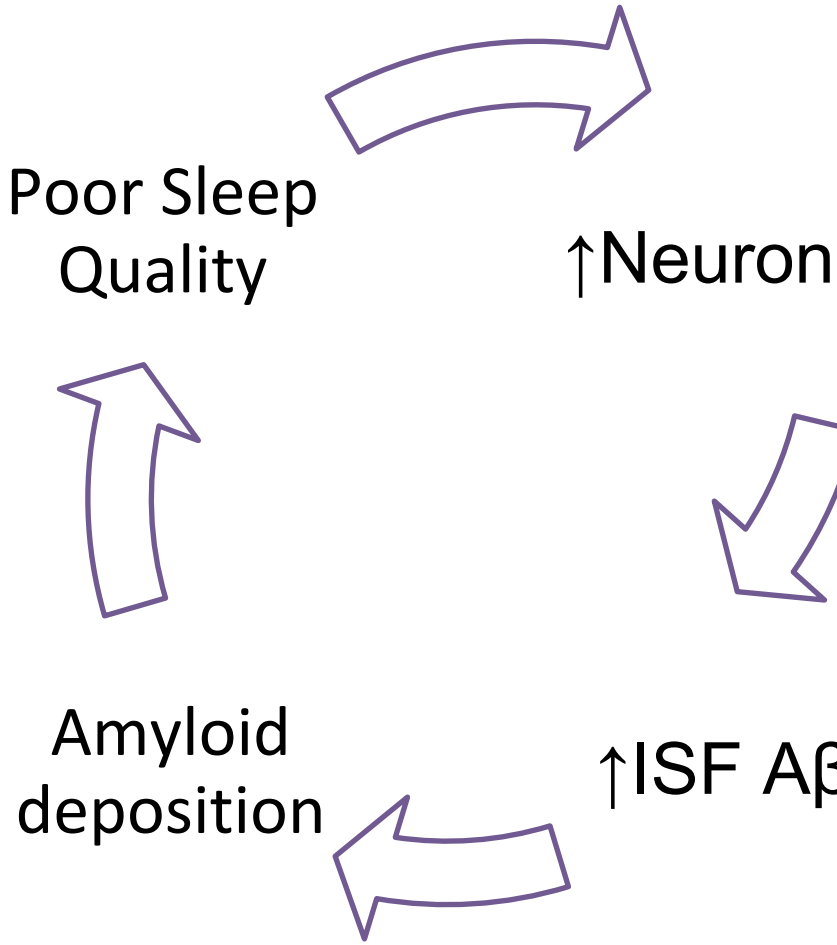
Spira et al., *SLEEP,* 2016;39:1121-8.

Prospective association of sleep duration with subsequent cortical thinning in cognitively normal older adults (*N* = 122).



Spira et al., *SLEEP,* 2016;39:1121-8.

Mechanisms?



Modified from Ju et al., 2014 (used here with further adaptation, courtesy of R. Osorio)

Summary & Conclusion

- Indices of poor sleep
  - Lower cognitive performance, cognitive decline
  - In vivo measures of amyloid burden and atrophy
- Sleep deprivation increases amyloid deposition
  - AD mouse model
  - AD *Drosophila* model
- Optimization of sleep and treatment of sleep disorders may play a role in AD and dementia prevention
- Longitudinal studies with objective sleep measures and repeated measurement of AD biomarkers are needed

Thank You

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