

 Conflict of I. I do not have any selling, or distributi patients, OR I. I do not have any selling, or distributi patients. 	Interest Disclosures for Speakers elationships with any entities producing, marketing, re- g health care goods or services consumed by, or used on, g relationships with entities producing, marketing, re- g health care goods or services consumed by, or used on,
Type of Potential Co	aflict Details of Potential Conflict
Grant/Research Sup	port
Consultant	
Speakers' Bureau	S
Financial suppor	t
Other	Stock - Cogentis Therapeutics, Inc.
X 3. The material press OR	nted in this lecture has no relationship with any of these potential conflicts,
4. This talk presents the following objection	material that is related to one or more of these potential conflicts, and re references are provided as support for this lecture:
1. 2. 3.	

ACCREDITATION STATEMENT

This activity has been planned and implemented in accordance with the accreditation requirements and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint providership of The American Academy of Sleep Medicine and The Virginia Academy of Sleep Medicine. The American Academy of Sleep Medicine is accredited by the ACCME to provide continuing medical education for physicians.





	H	J۷	VI	ЧU	CH	SI	HC)U	LD	W	ES	LE	EP	?			
				Reco	mmende	d hou	rs	May	be appro	priate		Not rec	omm	ended			
Older adults (>65 years)	<	5		5-6	7-8	9										>10	
Adults (26-64 years)		6		6	7-9	•	10									>10	
Young adults (18-25 years)	<	6		6	7-9	,	10	-11								>11	
Teenagers (14-17 years)	<	7			7	8-1	D	11								>11	
School-aged children (6-13 years)	<	7			7-8		9-11		12							>12	
Pre-schoolers (3-5 years)	<	8				8-9		10-	13	14						>14	
Toddlers (1-2 years)	<	9					-10		11-14		15	16				>16	
Infants (4-11 months)	<	10					10	-11		12-15		16	5-18			>18	
Newborns (0-3 months)	<	11							11-13		14-	17		18-19		>19	
1	2 3	4	5	6	7 8	9	10 1	1 1	2 13	14 1	15 16	5 17	18	19	20	21 22	23





In peace and war, the lack of sleep works like termites in a house: below the surface, gnawing quietly and unseen to produce gradual weakening which can lead to sudden and unexpected collapse.

—Major General Aubrey Newman (Follow Me, 1981)



DOES CHRONIC SLEEP DEPRIVATION TRIGGER NEURODEGENERATION?



nave increased	1 risk of de	ementia	
	Mild Cognitive Impairment or Dementia,	OR (9	5% CI)
	No. (%) (n = 107)	Unadjusted	Adjusted ^a
Hypoxia and Di	sordered Breathing N	Measures	
<15 Oxygen desaturation index, events/h	46 (43.0)	1 [Reference]	1 [Reference]
≥15	60 (56.1)	1.67 (1.03-2.69)	1.71 (1.04-2.83)
Oxygen saturation <90%			
<1% of sleep time	64 (59.8)	1 [Reference]	1 [Reference]
≥1% of sleep time	43 (40.2)	0.87 (0.54-1.41)	0.83 (0.51-1.38)
Sleep time in apnea or hypopnea, % Low (median: 0.9 [range, 0-2.2])	31 (29.0)	1 [Reference]	1 [Reference]
Mid (median: 4.4 [range, 2.3-7.0])	31 (29.0)	1.00 (0.55-1.82)	1.16 (0.61-2.20)
the first of the get and the			





Science 326, 1005-1007. 13 November 2009.

Amyloid-β Dynamics Are Regulated by Orexin and the Sleep-Wake Cycle

Jae-Eun Kang,¹ Miranda M. Lim,¹ Randall J. Bateman,^{1,2,3} James J. Lee,¹ Liam P. Smyth,¹ John R. Cirrito,^{1,2} Nobuhiro Fujiki,⁴ Seiji Nishino,⁴ David M. Holtzman^{1,2,3,5*}







Science 363, 880–884 (2019) 22 February 2019.

The sleep-wake cycle regulates brain interstitial fluid tau in mice and CSF tau in humans

Jerrah K. Holth^{1,2*}, Sarah K. Fritschi^{1,2*}, Chanung Wang^{1,2}, Nigel P. Pedersen^{3,4}, John R. Cirrito^{1,2}, Thomas E. Mahan^{1,2}, Mary Beth Finn^{1,2}, Melissa Manis^{1,2}, Joel C. Geerling⁵, Patrick M. Fuller⁶, Brendan P. Lucey^{1,2}, David M. Holtzman^{1,2}†



How do toxic metabolites exit the Blood Brain Barrier (BBB)?







Milestones in BBB physiology

- 1813 Paolo Mascagni reports CNS-Dural lymphatics
- 1856 Rudolph Virchow, Charles-Philippe Robin describe perivascular spaces
- 1885 Paul Ehrlich, Injections of Trypan Blue
- 1898 Arthur Biedl, described BBB concept, PMJ
- 1918 Stern L, "barrière hémato-encéphalique"
- 1981 Cserr H, describes ISF flow in perivascular spaces
- 2013 Xie L, connect ISF exchange to sleep cycle
- 2015 Louveau & Kipnis 2015 Meningeal Lymphatics re-described













15













		HR (95% CI)	p-value					
	55-64 years, reference NTT (n=10,281)							
	mild TBI (n=1,226)	1.08 (.77–1.49)	.665					
	moderate/severe TBI (n=2,769)	1.65 (1.35–2.02)	<.001					
Concussion patients	65–74 years, reference NTT (n=8,607)							
bayo incroasod rick	mild TBI (n=850)	1.22 (1.02–1.47)	<.05					
of dementia	moderate/severe TBI (n=2,750)	1.50 (1.33–1.68)	<.001					
	75–84 years, reference NTT (n=10,025)							
	mild TBI (n=938)	1.26 (1.13–1.42)	<.001					
	moderate/severe TBI (n=4,347)	1.38 (1.29–1.47)	<.001					
JAMA Neurology Gardner RC et al. 2014. Dec	85+ years, reference NTT (n=4,218)							
	mild TBI (n=422)	1.25 (1.09–1.44)	<.005					
	moderate/severe TBI (n=2,278)	1.31 (1.21–1.41)	<.001					





Neuronal P-tau accumulation after TBI - WORSE in *Aqp4* knockout mice. TBI (Ipsilateral) Control Wild Type Aqp4-/-**Cerebral Cortex** В Α P-Tau P-Tau P-Tau D **Cerebral Cortex** Ε Striatum Contralateral Contralateral Ipsilateral Ipsilateral (%) Area Fraction (%) Area Fraction (10-5 WT Agp4 WT Agp4

Anatomy of Cerebral Microvasculature



Reina de la Torre, et al Anat Record 1998;251:87-96









*Unpublished Data Characteristic	Controls no TBI, <u>good</u> <u>sleepers</u> (N=24)	Controls no TBI, <u>poor</u> <u>sleepers</u> (N=14)	p-value	Cases TBI, <u>good sleepers</u> (N=51)	Cases TBI, <u>poor sleepers</u> (N=62)	p-value
PSQI score, mean (SD)	4.4 (2.8)	14.2 (2.8)	10-10	5.8 (2.1)	13.6 (2.9)	10-30
Age, mean (SD), y	38 (12.4)	41 (8.4)	0.328	39 (10.7)	39 (12.2)	0.884
Male, no. (%)	21 (84)	11 (79)	0.693	44 (86)	57 (92)	0.371
BMI, mean (SD)	29(4.9)	29 (3.7)	0.772	29 (5.2)	32 (5.6)	0.069
Years since TBI, mean (SD)	n/a	n/a	n/a	11.2 (8.8)	12.3 (7.8)	0.122
Hours of sleep, mean (SD)	6.5 (1.0)	5.1 (1.3)	0.049	6.8 (1.6)	4.6 (1.1)	10-12
STOP-BANG score, mean (SD)	2.38 (1.28)	2.81 (1.8)	0.040	2.8 (1.59)	3.9 (1.76)	0.00087



SLEEP REGULATED GLYMPHATIC EVIDENCE IN HUMANS?











PRELIMINARY MRI EVIDENCE OF GLYMPHATIC EXCHANGE CURRENTS

- Collaboration with GE-Research and Walter Reed
- 3T experimental "MAGNUS" (head-only, Microstructure Anatomy Gradient for Neuroimaging with Ultrafast Scanning) MRI
- ultra low V_{ENC} (0.24mm/s)
- High slew rates (500T/m/s)
- Peripheral pulse-gated diffusion

























Battalion to hold sleep deprivation awareness brief at 0430

"The unit won't rest until the problem is solved. These driving accidents aren't something we're going to take lying down," LTC Newman commented. "We're working around the clock to remedy this sleep deprivation."

"If they can't find eight consecutive hours to sleep between midnight and four in the morning, that's on them," Newman said before scooping his pre-workout powder into a can of Monster.

DUFFELBLOG

