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USU Uniformed Services University

POOR SLEEP CORRELATES WITH BIOMARKERS OF NEURODEGENERATION IN MILD TRAUMATIC BRAIN INJURY

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5 MAY 2021

DISCLOSURES/DISCLAIMERS

The authors have no conflicts of interest to disclose

Grant funding for this project is from:
Dept of Defense, Chronic Effects of Neurotrauma Consortium (CENC) Award W81XWH-13-2-0095
Dept of Veterans Affairs CENC Award I01 CX001135, NIH, National Institute of Nursing Research Intramural Research Program.

In addition Dr. Werner receives grant funding funding from NIH (NIA) and is part owner and founder of Cogentis Therapeutics, both unrelated to this presentation.

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OBJECTIVES

Traumatic brain injury's link to dementia

Glymphatic exchange: Sleep link to dementia

Biomarker Data exploring both

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*L*ONG-TERM *I*MPACT *M*ILITARY-RELEVANT *B*RAIN *I*NJURY *C*ONSORTIUM *C*HRONIC *E*FFECTS OF *N*EUROTRAUMA *C*ONSORTIUM

The mission of the LIMBIC-CENC is to fill the gaps in knowledge about the basic science of mTBI (also termed concussion or mild TBI), determine its effects on late-life outcomes and neurodegeneration, identify service members most susceptible to these effects, and identify the most effective treatment strategies.

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MILD TRAUMATIC BRAIN INJURY LINKS TO DEMENTIA

PROSPECTIVE STUDY OF DEMENTIA RISK AFTER TBI

Much of the evidence for an association has come from Epidemiologic studies- few prospective and majority retrospective

WW II Navy and Marine Veterans 1944 - 1945

548 hospitalized for non-penetrating TBI 1228 hospitalized for non-TBI injuries

Evaluated 1996 – 1997 through telephone interviews and clinical assessments

Severe TBI (LOC or PTA > 24 hours)

HR 4.51 (95% CI 2.09 – 9.63) for AD

Moderate TBI (LOC or PTA > 30 min, < 24 h)

HR 2.39 (95% CI 1.24 – 4.58) for AD

Mild TBI (LOC or PTA < 30 min)

HR 0.76 (95% CI 0.51 – 3.47)

Plassman et al, *Neurology* 2000;55:1158-1166

SUMMARY OF LITERATURE ON DEMENTIA AFTER TBI

Multiple retrospective and increasing prospective studies indicating TBI in early to mid-life increase risk of dementia

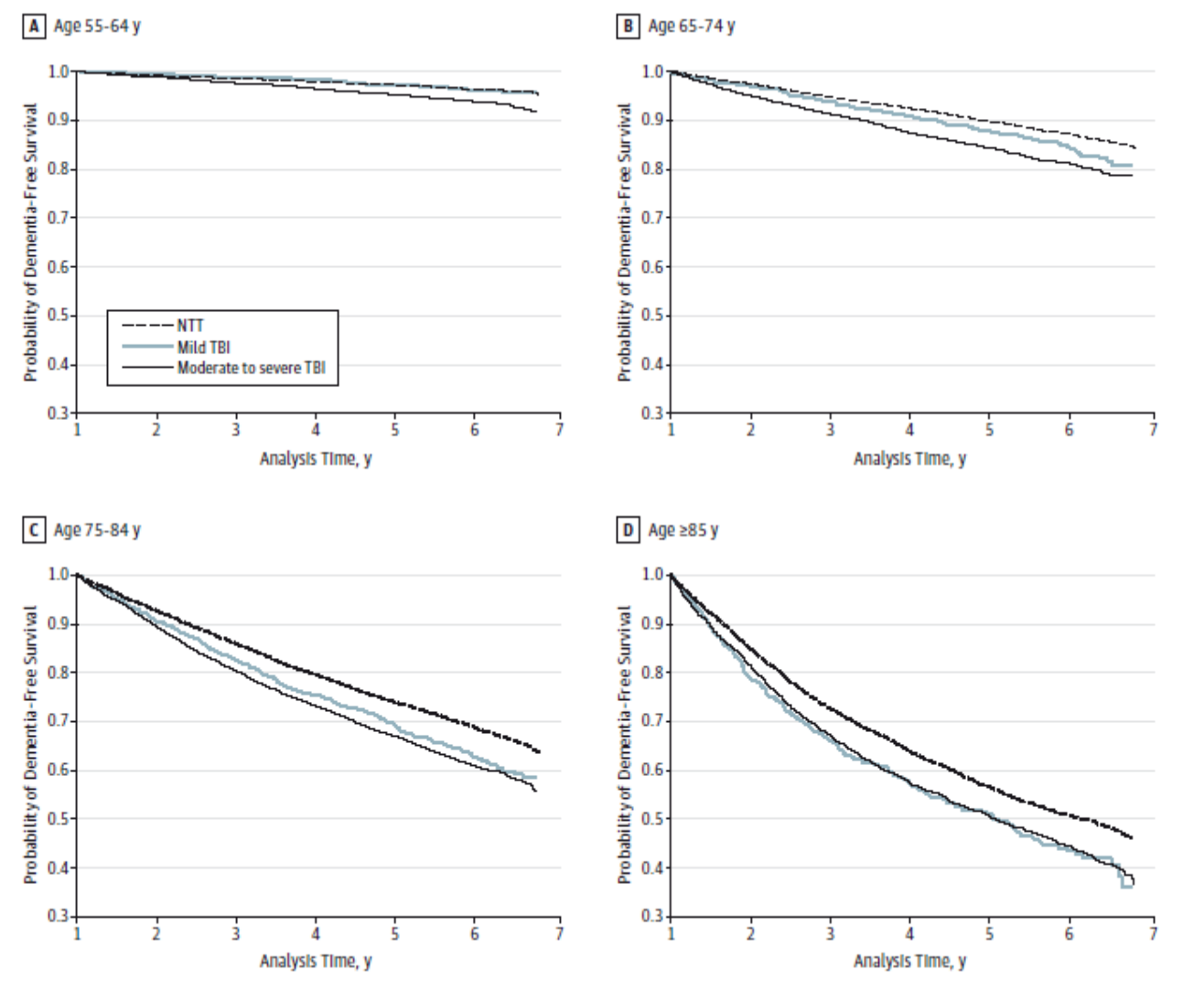
- IOM: "There is sufficient evidence of an association between moderate and severe TBI and dementia…limited/suggestive evidence of an association between mild TBI (with loss of consciousness) and dementia…[and] inadequate/insufficient evidence to determine whether an association exists between mild TBI (without loss of consciousness) and dementia."

Assumption has long been that TBI increases risk of AD

- Few careful studies examining pathology or detailed clinical features

Institute of Medicine Committee on Gulf War and Health. *Gulf War and Health, Volume 7: Long-Term Consequences of Traumatic Brain Injury.* Washington, D.C.: National Academies Press, 2009.

POPULATION BASED STUDY: CALIFORNIA DEMENTIA RISK AFTER TBI VS. NON-BRAIN TRAUMA



Gardner et al, *JAMA Neurol* 2014;71:1490-1497

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TBI PATIENTS HAVE INCREASED RISK OF DEMENTIA

JAMA Neurology

Gardner RC et al. 2014. Dec.

	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
65–74 years, reference NTT (n=8,607)		
mild TBI (n=850)	1.22 (1.02–1.47)	<.05
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
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

MTBI LOC ASSOCIATED WITH 2-FOLD INCREASED DEMENTIA RISK IN VETERANS

- First epidemiological study through VA healthcare system
- Largest epidemiological study to date
- TBI diagnosis through clinical evaluations for subset (CTBIE database, N = 27,425 of 357,558 total)
- HRs showed a dose effect based on TBI severity

Figure. Cumulative Incidence of Dementia by Traumatic Brain Injury (TBI) Severity

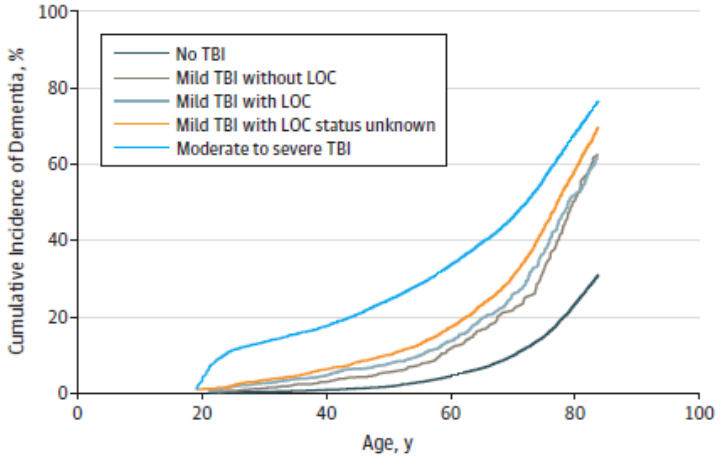

Table 2. Unadjusted and Adjusted Risk of Dementia by Traumatic Brain Injury Severity (N = 357 558)

Model	Individuals Without TBI (n = 178 779)	Individuals With ≥1 TBI (n = 178 779)	Participant Group, Hazard Ratio (95% CI)[a] Mild TBI Without LOC (n = 17 759)	Mild TBI With LOC (n = 23 097)	Mild TBI With LOC Status Unknown (n = 55 004)	Moderate to Severe TBI (n = 82 919)
Unadjusted	1 [Reference]	3.41 (3.29-3.53)	2.29 (2.04-2.58)	2.48 (2.26-2.72)	3.11 (2.97-3.25)	3.75 (3.61-3.89)
1[b]	1 [Reference]	3.41 (3.30-3.53)	2.32 (2.06-2.61)	2.49 (2.27-2.73)	3.14 (3.00-3.28)	3.73 (3.60-3.88)
2[c]	1 [Reference]	3.41 (3.29-3.53)	2.34 (2.08-2.63)	2.50 (2.28-2.75)	3.16 (3.02-3.31)	3.71 (3.57-3.85)
3[d]	1 [Reference]	3.45 (3.33-3.57)	2.36 (2.10-2.66)	2.51 (2.29-2.76)	3.19 (3.05-3.33)	3.77 (3.63-3.91)

Abbreviations: LOC, loss of consciousness; TBI, traumatic brain injury.

[a] No TBI is the reference group; *P* values in all other cells are <.001.

[b] Model 1 is adjusted for demographic characteristics (sex, race, education, and income).

[c] Model 2 is adjusted for demographic characteristics and medical conditions (diabetes, hypertension, myocardial infarction, cerebrovascular disease, and peripheral vascular disease).

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Barnes et al, *JAMA Neurol* 2018 doi:10.1001/jamaneurol.2018.0815

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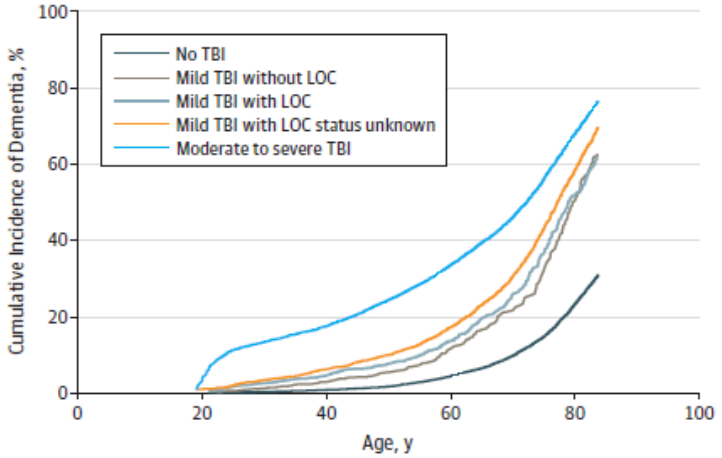

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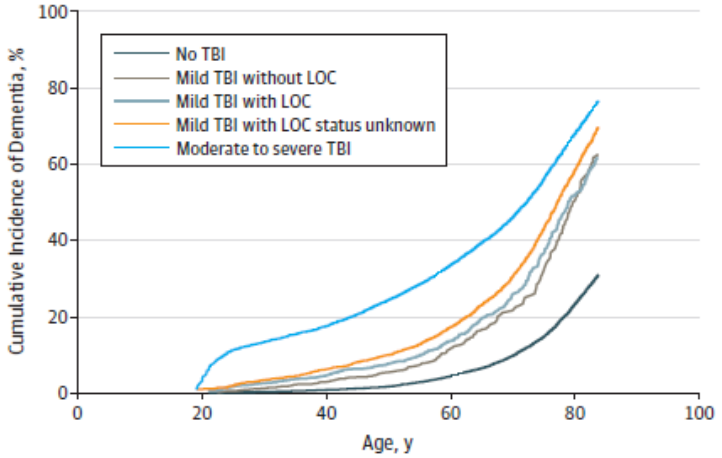

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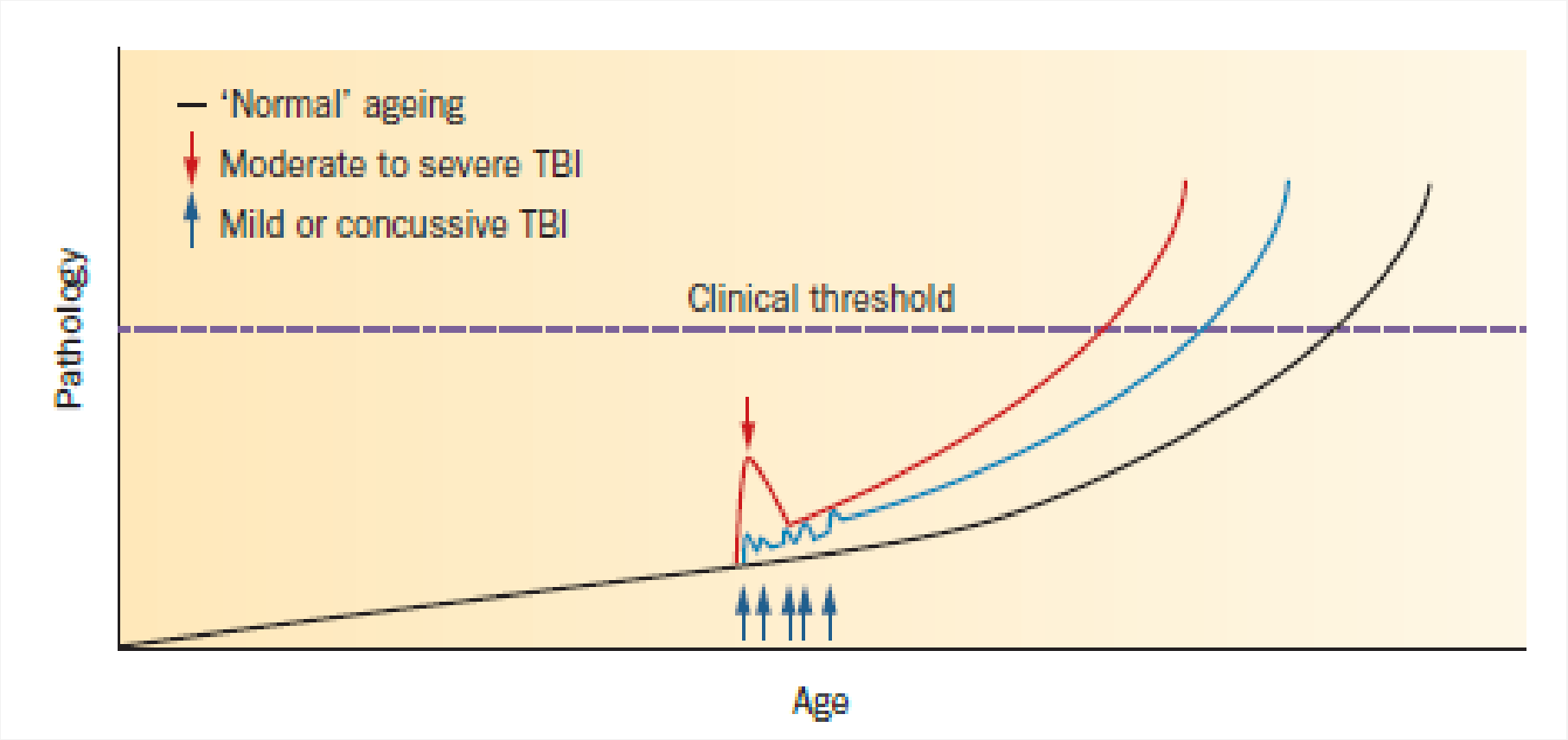
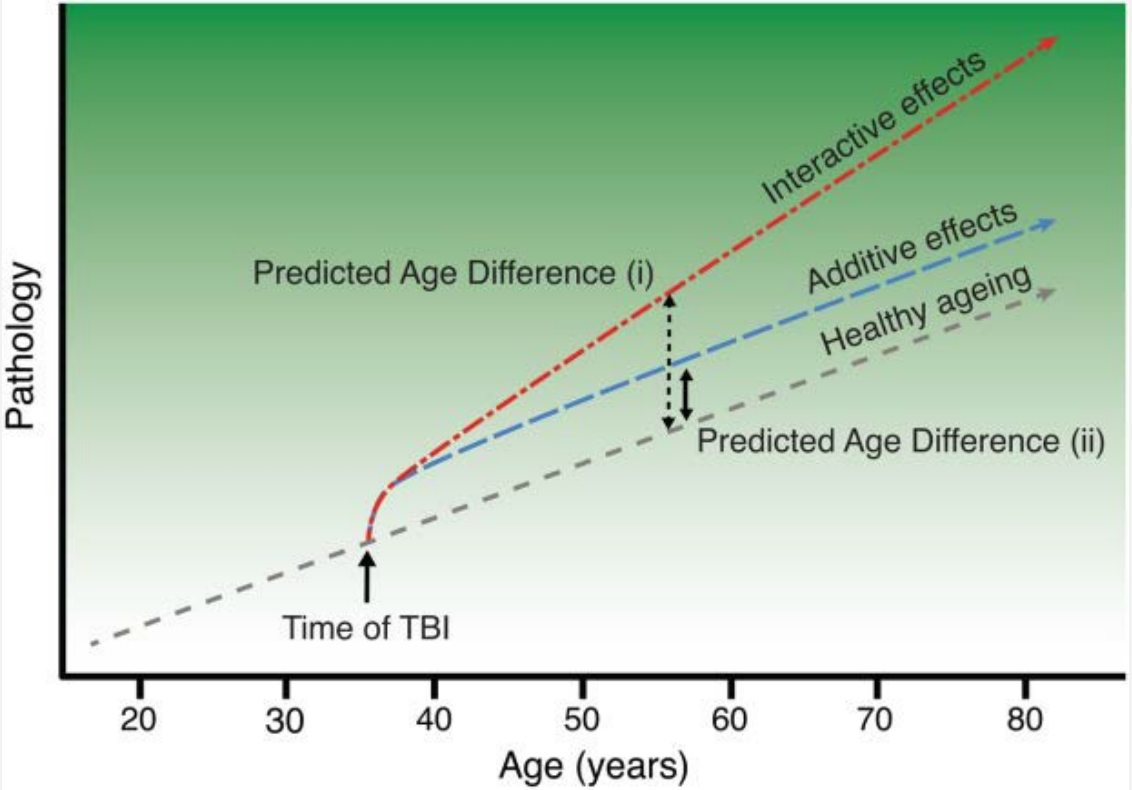
Barnes et al, *JAMA Neurol* 2018 doi:10.1001/jamaneurol.2018.0815

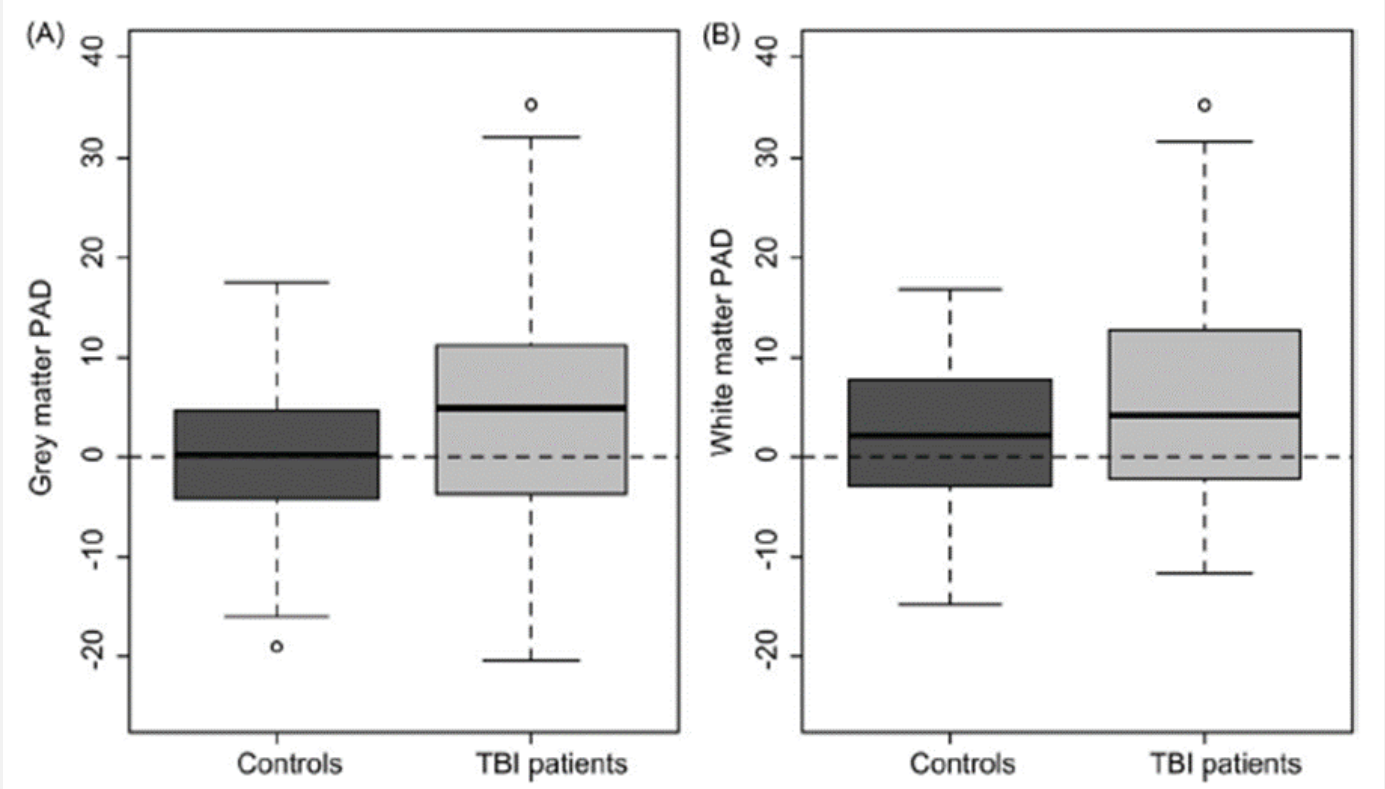
LIMBIC CENC INTERACTION BETWEEN TBI AND AGING: A HYPOTHESIS



DH Smith et al, *Nature Rev. Neurol.* 2013;9:211-221

ACCELERATED BRAIN ATROPHY AFTER TBI





Cole JH, *Ann Neurol* 2015;77:571-581

DEPLOYMENT-RELATED MTBI & REMOTE DEMENTIA KNOWLEDGE GAPS

While there is rapidly increasing epidemiological data to support a link between combat-related TBI and remote onset dementia, the underlying pathomechanism(s) have not yet been established. Current critical knowledge gaps required to both prevent and develop targeted therapy are the following:

1) Full characterization of neuropathology of TBI-related dementia
2) Full characterization of pathomechanisms underlying TBI-related dementia
3) **fluid biomarkers for (pre-clinical) diagnosis and treatment of TBI-related dementia**

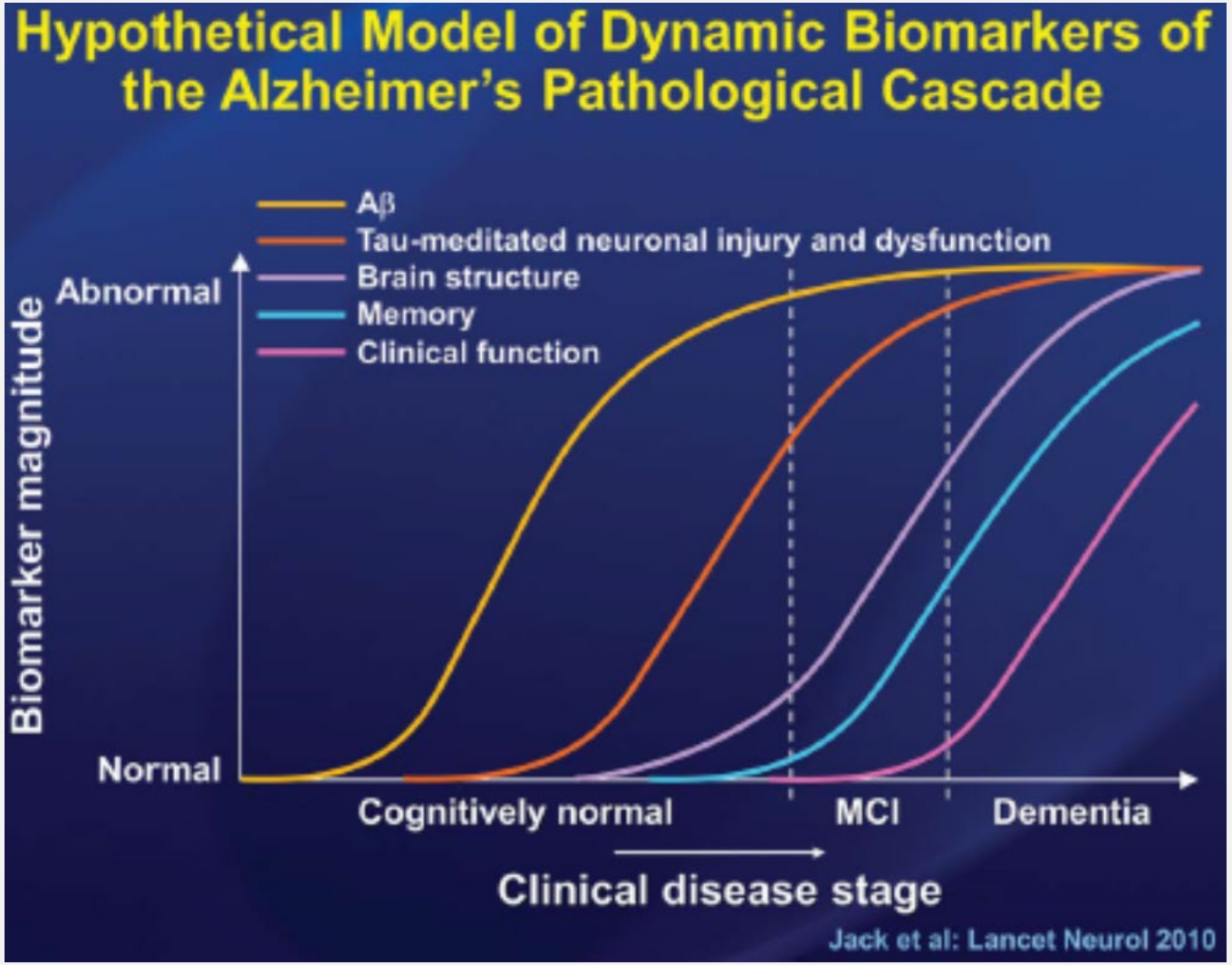
PROPOSE: TBI outcome Biomarker Discovery Project among CENC cohort

FDA BIOMARKER DEFINITIONS

1. **Diagnostic**
   Objective indicator of medical state observed externally accurately and reproducibly
2. **Prognostic**
   Indicator of future clinical course in the absence of a treatment or intervention
3. Predictive
   Measurable baseline characteristic(s) that categorize patients according to their likelihood of response to a particular treatment.
4. Pharmacodynamic
   Dynamic measurements which show that biologic response has occurred in a patient after a therapeutic intervention through target engagement.

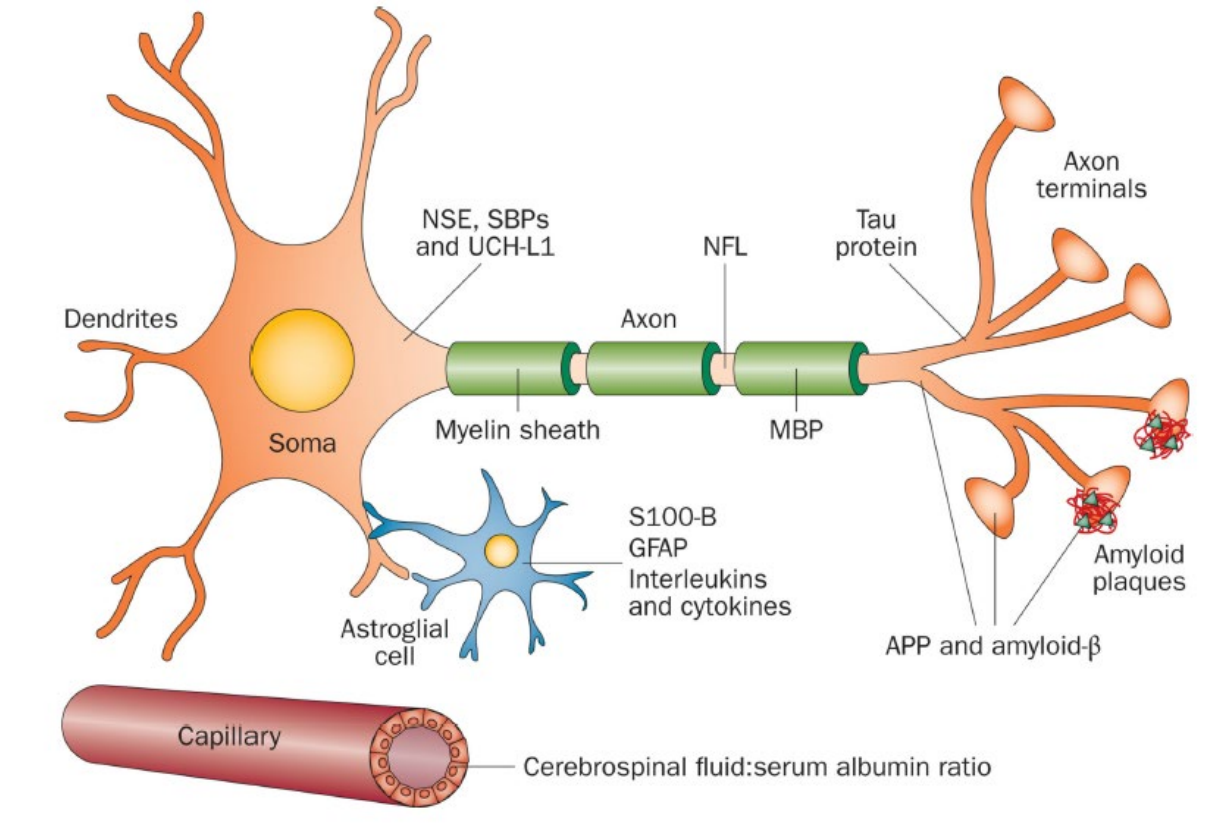
From Califf, Exp Biol Med 2018, 243(3):213-221.

BACKGROUND: BIOMARKERS IN ALZHEIMERS DISEASE



- Dynamic AD Biomarkers used in AD research
- Need quantifiable biomarkers that: 1) reflect pathology; and 2) become abnormal in pre-clinical stage for effective therapies to be developed
- In AD, Aβ changes earliest measurable, but clinical sxs correlate with tau deposits
- Aβ RCTs successful in lowering Aβ, but no effect on clinical outcomes

BACKGROUND: CANDIDATE TBI BIOMARKERS



From Zetterberg et al, Nat Rev Neur 2013

Neurons:

- NSE, SBPs and UCH-L1: neuronal cytoplasm.
- NFL: neuronal large-calibre myelinated axons.
- Tau: neuronal thin nonmyelinated axons.
- APP and amyloid-β: produced in axon terminals. (diffuse amyloid plaques).

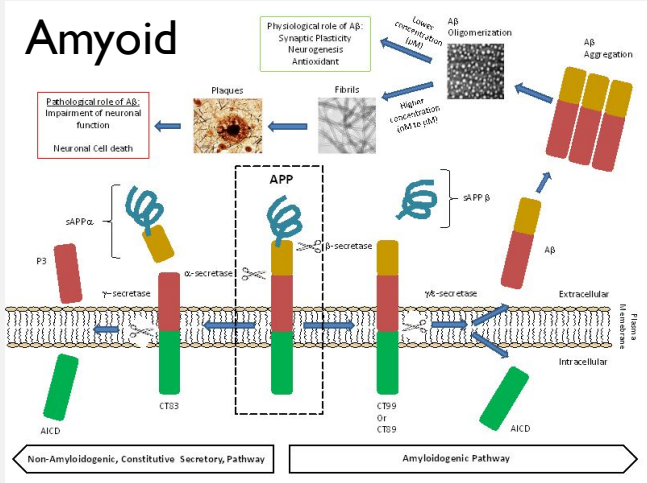
Astrocytes & Glia:

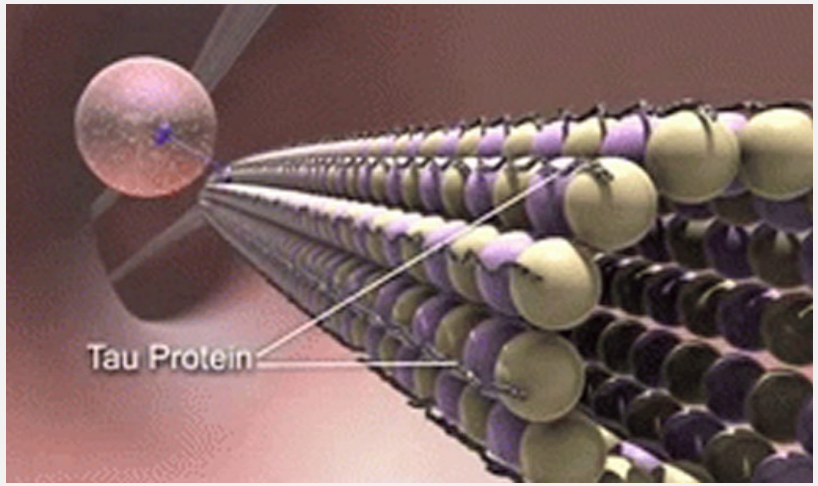
- S100-B
- GFAP,
- Inflammatory cytokines (e.g. IL-6, IL-10, TNF-α)

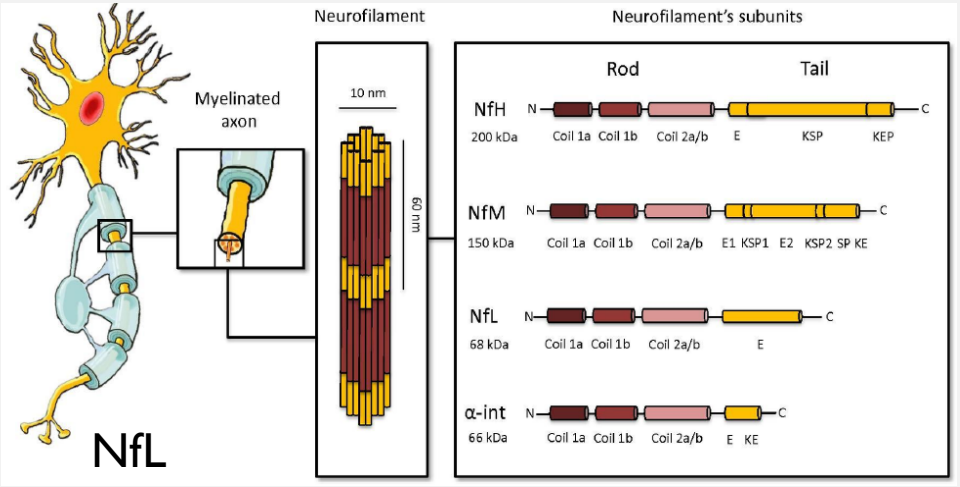
Vascular:

- VEGF
- vWF
- ICAM
- ANG-1

CANDIDATE TBI-DEMENTIA BIOMARKERS: AMYLOID, TAU & NFL







- Transmembrane glycoprotein
- Underdetermined function
- Aggregates/plaque associated with disease
- Markedly elevated after acute TBI
- Associated with AD

From Cardenas-Aguayo et al.
DOI: 10.5772/57398 2014

- Neuronal structural protein
- Stabilizes axonal cytoskeleton
- High plasma levels in acute TBI correlate with worse outcomes
- Phosphorylated in diseased states
- Associated c neurodegenerative disorders (CTE, AD, FTD)

From Gaetani et al. JNNP 2019

- Neuronal cytoplasmic protein expressed in large caliber myelinated axons (CNS/PNS)
- Associated with axonal damage
- Age, but not sex dependent in healthy population
- Promising diagnostic/prognostic biomarker neurodegenerative disorders (AD, HD, PD, ALS, MS, CMT among others)

From Rosen et al., CSF in Clin Neur 2015

TBI BIOMARKERS, CHRONIC STAGE, PRIOR STUDIES

Few biomarker studies of chronic/remote TBI effects :

- Olivera et al, JAMA Neurology, 2015 (SIMOA)
  - 70 AD mTBI (MAMC), up to 16 mo post-deployment, ↑ plasma tau in repetitive TBI and ↑ correlated with NSI
- Stern et al, J AD, 2016
  - 78 Retired NFL, ↑ exosomal tau and ↑ **correlated with PSI & verbal memory,** but not depression or symptoms
- Rubinstein et al, JAMA Neurology 2017 (SOFIA)
  - ↑ plasma p-tau/t-tau ratio in 21 TBI (1-8 mos) compared to HC
- Gill et al, Brain Injury, 2018 (SIMOA)
  - 42 AD mTBI (MAMC), ↑ CNS-derived exosomal tau/Aβ42/IL-10 and exo tau correlated with NSI

LIMBIC CENC BIOMARKER DISCOVERY PROJECT

- Interim analysis of 200 well-characterized CENC Longitudinal Study subjects (100 mTBI with LOC/PTA, 50 mTBI with AOC only, 50 TBI negative) using ultrasensitive assays from plasma and peripherally circulating exosomes, and correlation with clinical outcomes, of following candidate chronic TBI biomarkers:
  - Neurodegeneration (Aβ40/Aβ42, total tau/p-tau, NFL)
  - Neuroinflammatory (IL-6, IL-10, TNF-α)
  - Vascular injury (VEGF)

METHODS- IN DEPTH CENC TBI CHARACTERIZATION

- CENC TBI characterization: modified OSU-TBI ID with each PCE further evaluated with VCU Retrospective Concussion Diagnostic Interview (VCU rCDI) to subgroup into:
  - mTBI vs TBI-neg
  - Total number lifetime mTBI
  - Total number blast TBI

- Enrolled subjects then undergo comprehensive baseline evaluation with interval f/u evaluations:
  - Neurobehavioral symptoms surveys (NSI, PCL-5, PHQ-9, PSQI)
  - Neuropsychological testing from TBI CDEs
  - Imaging
  - Research blood draw

BIOMARKER ANALYSIS
ULTRASENSITIVE IMMUNOASSAY

Plasma proteins examined for 9 candidate biomarkers by SIMOA

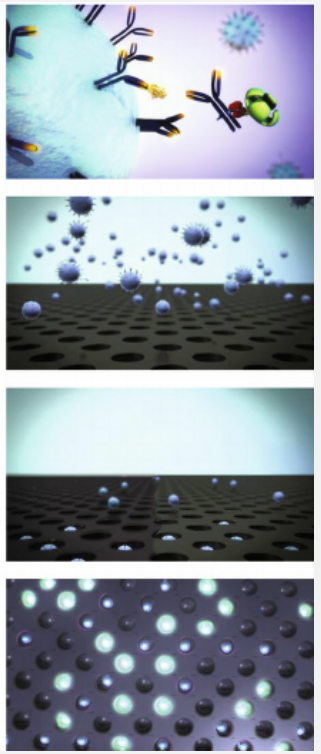
Courtesy of Quanterix.com

Standard paramagnetic particles coupled with antibody designed to bind a specific protein target are added to the sample to form a traditional immunocomplex.

Beads are subsequently concentrated and washed. When low abundance biomarkers are present, there are many more beads than targeted proteins. Each bead will only contain one bound protein or none.

Beads are then loaded into microarrays in the presence of substrate. Each array consists of >200k microwells, each large enough to hold only one bead. An oil solution is added to seal each well and remove excess beads.

Within the sealed femotliter-sized wells, a single target molecule quickly generates enough fluorescence signal to be easily measured. Positive wells are enumerated to determine protein concentration.



Courtesy of Quanterix.com

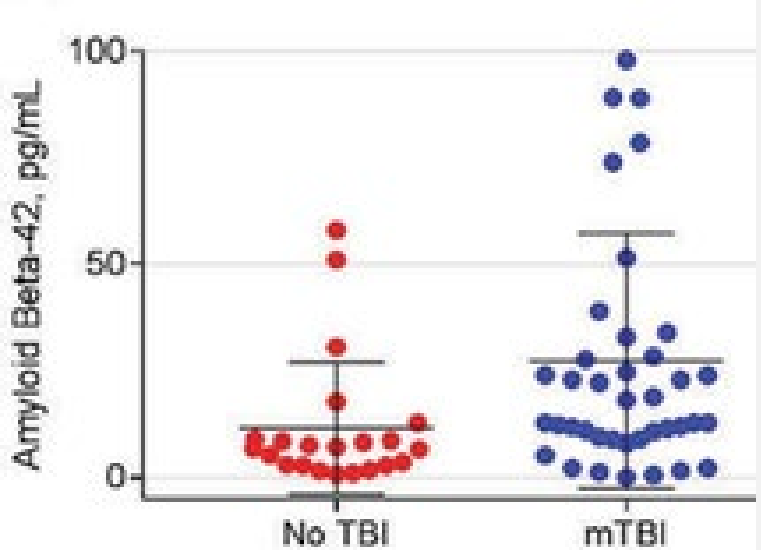
300-1,000 times greater sensitivity than conventional ELISA

DEMOGRAPHICS

Repetitive TBI group similar demographically to non-repetitive TBI group, but also with significant differences in symptom measures:

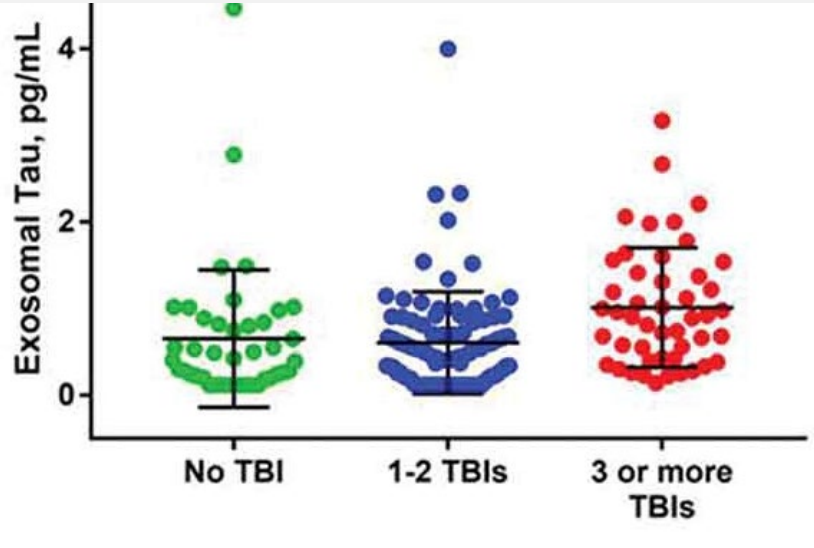
Characteristic	Controls	Cases		Significance	*p*-Value
	No TBI (*n* = 45)	Less than three TBI (*n* = 94)	Three or more TBI (*n* = 56)		
Age, mean (SD) (year)	39.91 (11.41)	40.34 (11.34)	39.55 (9.77)	$F_{2, 192} = 0.096$	0.908
Male, no. (%)	38 (84.4)	82 (87.2)	47 (83.9)	$X^2 = 0.380$	0.827
Education, no. (%)					
High school graduate or GED	5 (11.1)	10 (10.6)	8 (14.3)	$X^2 = 0.860$	0.930
Some college or technical training	19 (42.2)	43 (45.7)	26 (46.4)		
College graduate or higher	21 (46.7)	41 (43.6)	22 (39.3)		
Number of TBI, mean (SD)	0.00	1.44 (0.499)	4.30 (1.71)	$F_{2, 192} = 265.53$	0.000
Number of blast TBI, mean (SD)	0.00	0.45 (0.56)	1.25 (1.15)	$F_{2, 192} = 39.57$	0.000
Number of general TBI, mean (SD)	0.00	0.99 (0.68)	3.05 (1.43)	$F_{2, 192} = 158.18$	0.000
Years since first TBI, mean (SD)		16.81 (11.53)	23.48 (10.67)	$F_{1, 148} = 14.44$	0.952
Years since last TBI, mean (SD)		11.78 (9.97)	7.27 (4.44)	$F_{1, 148} = 10.23$	0.002
PHQ-9 total, mean (SD)	5.42 (5.78)	9.37 (6.48)	9.98 (6.09)	$F_{2, 190} = 7.94$	0.001*
PCL-M total, mean (SD)	18.13 (17.96)	29.68 (19.68)	33.30 (19.59)	$F_{2, 189} = 8.29$	0.000*
NSI, mean (SD)					
NSI total	16.64 (15.29)	28.00 (16.50)	34.80 (14.71)	$F_{2, 190} = 16.66$	0.000
Somatic	3.64 (4.48)	7.00 (4.90)	9.69 (4.81)	$F_{2, 190} = 19.80$	0.000
Affective	7.04 (5.82)	10.65 (6.20)	11.93 (5.13)	$F_{2, 191} = 9.30$	0.000*
Cognitive	3.53 (3.53)	5.84 (3.98)	7.04 (3.60)	$F_{2, 191} = 10.90$	0.000*
Vestibular	1.18 (1.89)	2.35 (2.44)	3.62 (2.25)	$F_{2, 191} = 14.46$	0.000

TRAUMATIC BRAIN INJURY ALSO CAUSES ELEVATIONS IN MARKERS OF NEURONAL INJURY AND DEGENERATION



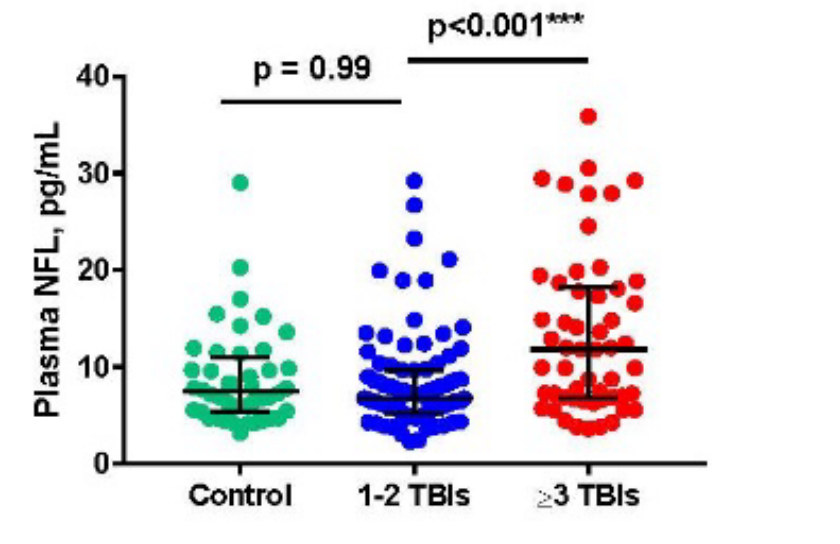
Amyloid Beta

Gill J et al. Brain Inj. 2018



Tau

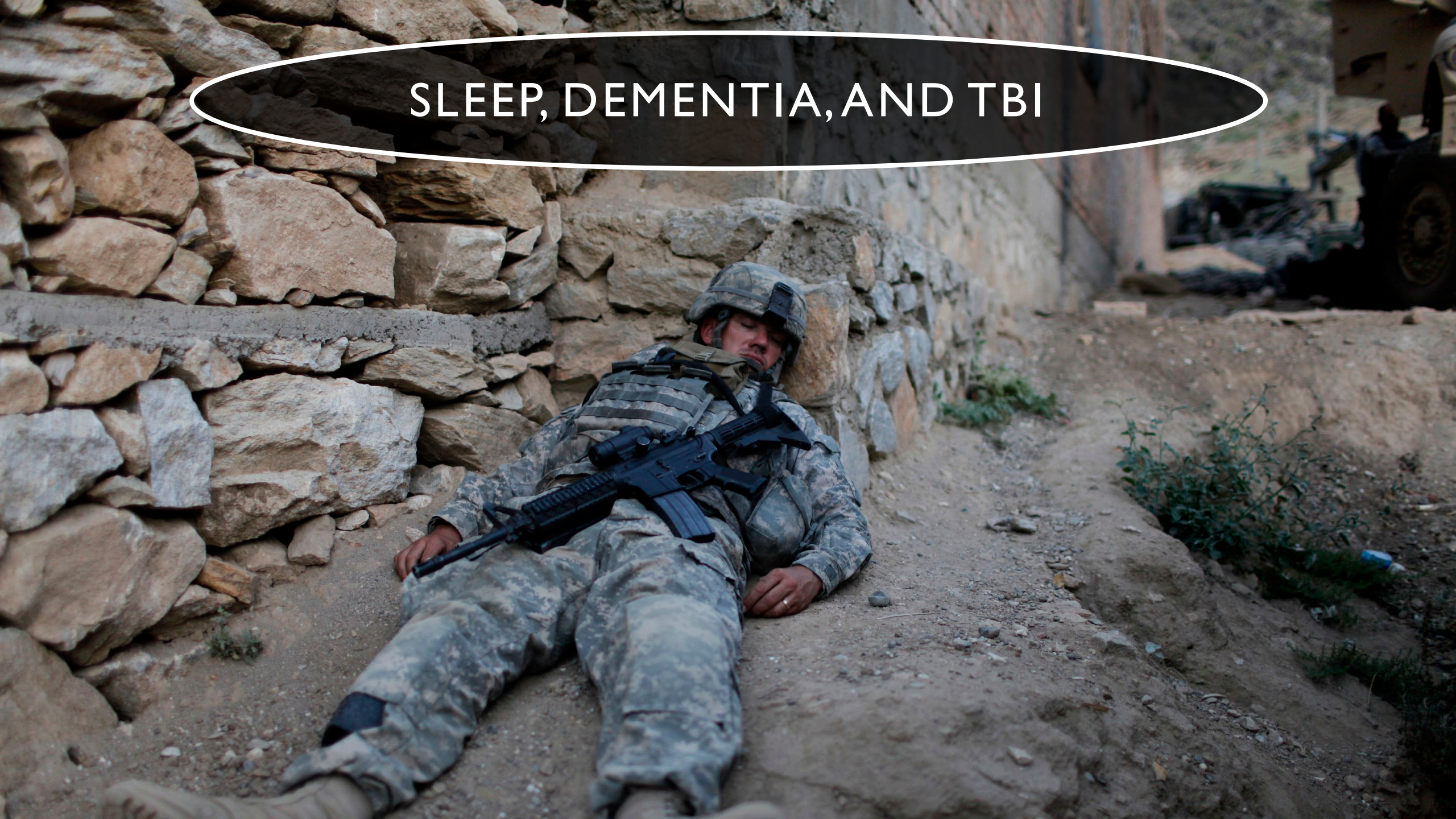
Kenney K, et al. Brain Inj. 2018.



Neurofilament Light (NfL)

Guedes et al. Neurology. 2020 May

SLEEP, DEMENTIA, AND TBI



LIMBIC CENC

WHY SLEEP IS NON-NEGOTIABLE

Synaptic downscaling for plasticity

Waste clearance via glymphatic system

Memory consolidation

Physical recovery

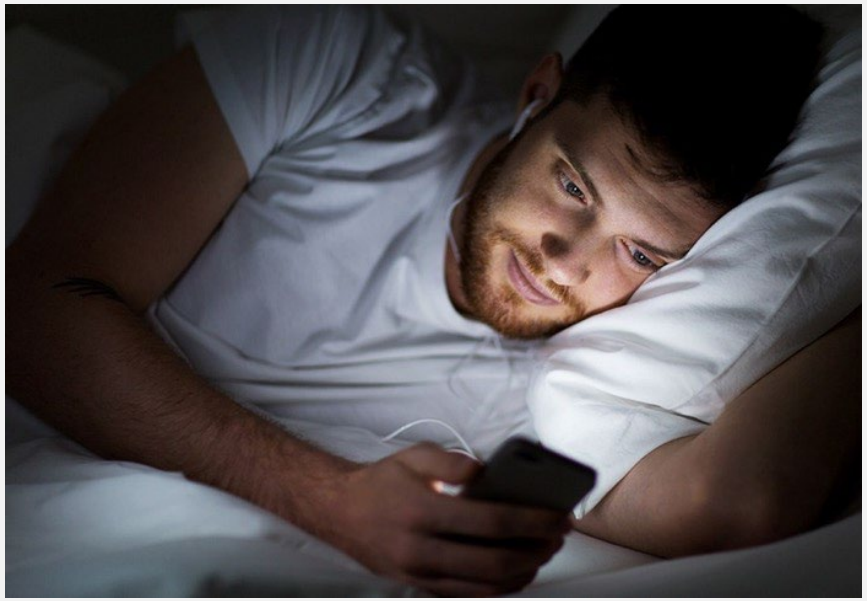
Growth (growth hormone release)

Parasympathetic activity (digestion,heart rate variablility, erectile tissue)

Immune regulation

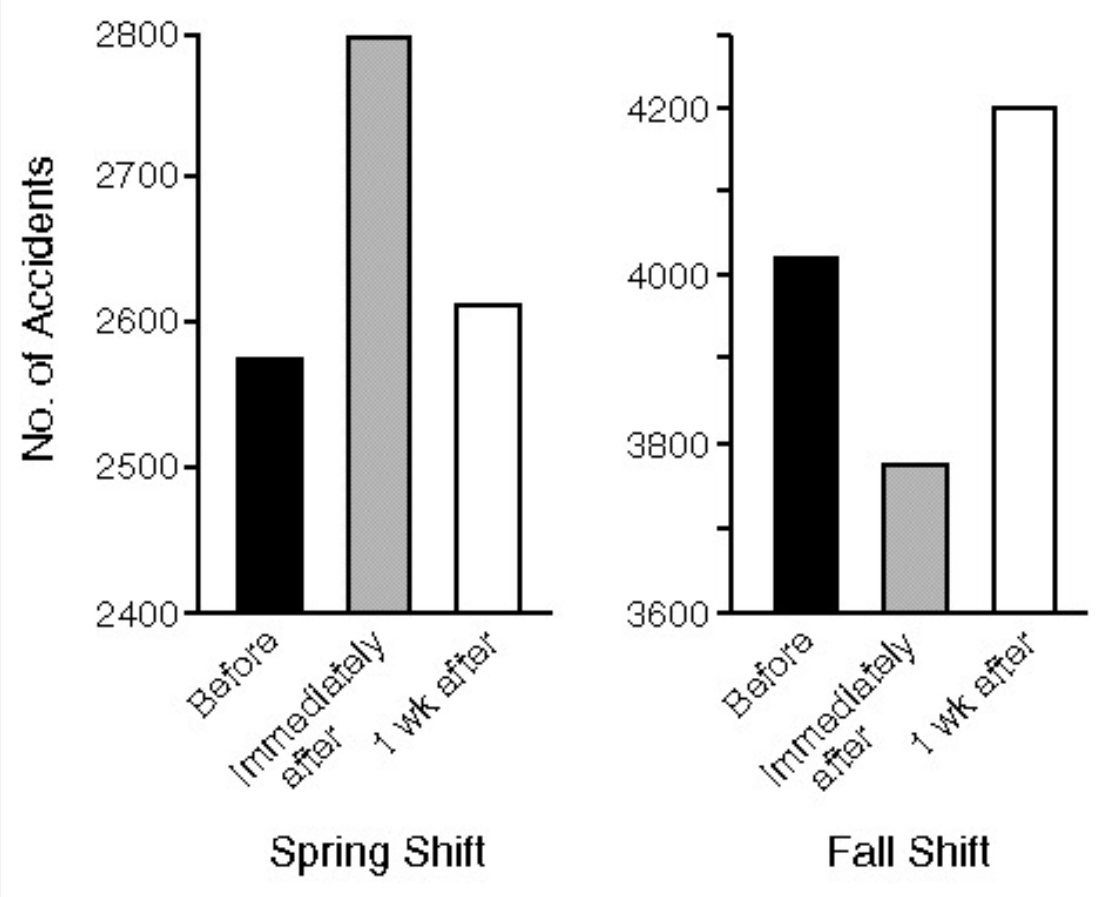
WE SLEEP LESS AND LESS….

- People in USA who sleep < 6 hours per night:
  - 12% 1990
  - 20% 2009
  - 35% 2014



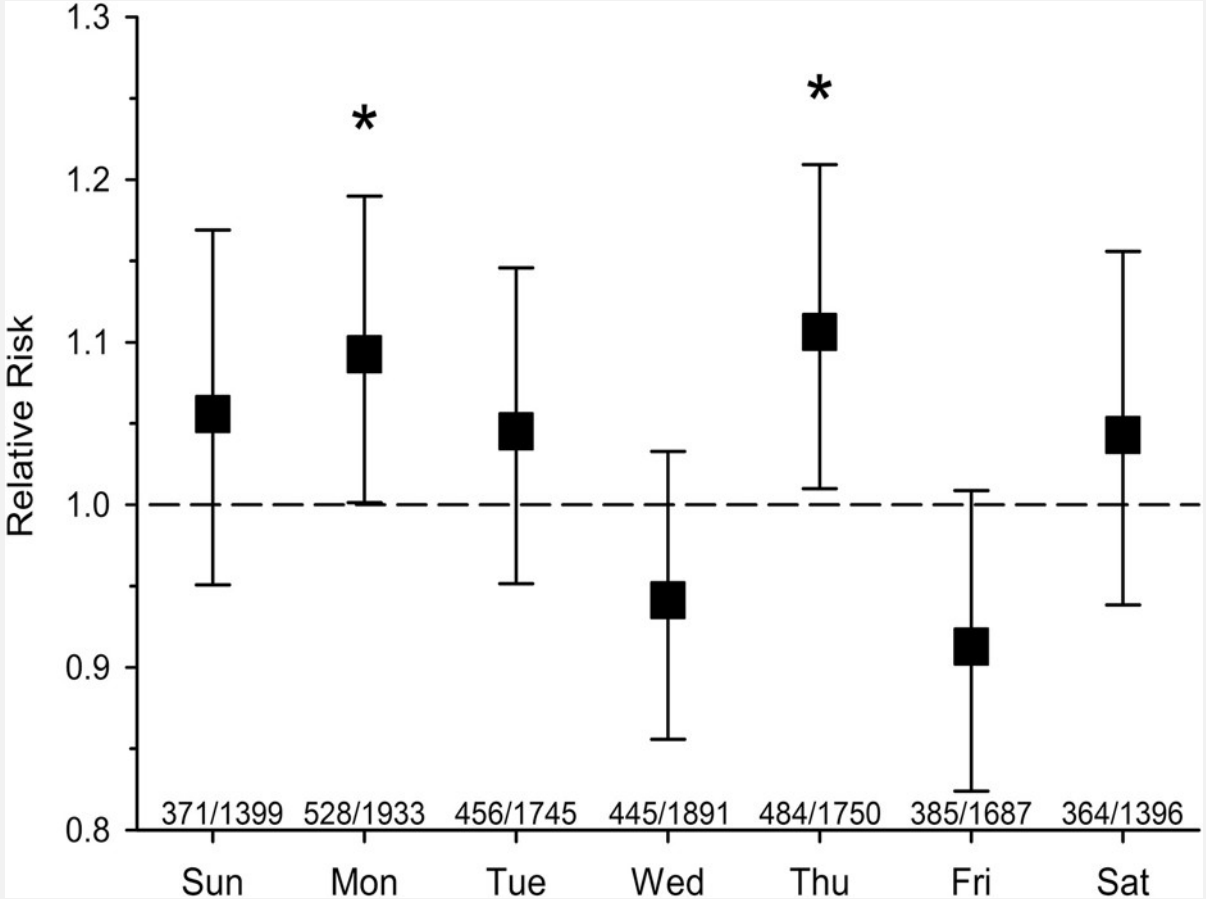
MMWR Morb Mortal Wkly Rep. 2016 Feb 19;65(6):137-41.

RISKS OF MISSING ONE HOUR OF SLEEP



Increased Car Crashes

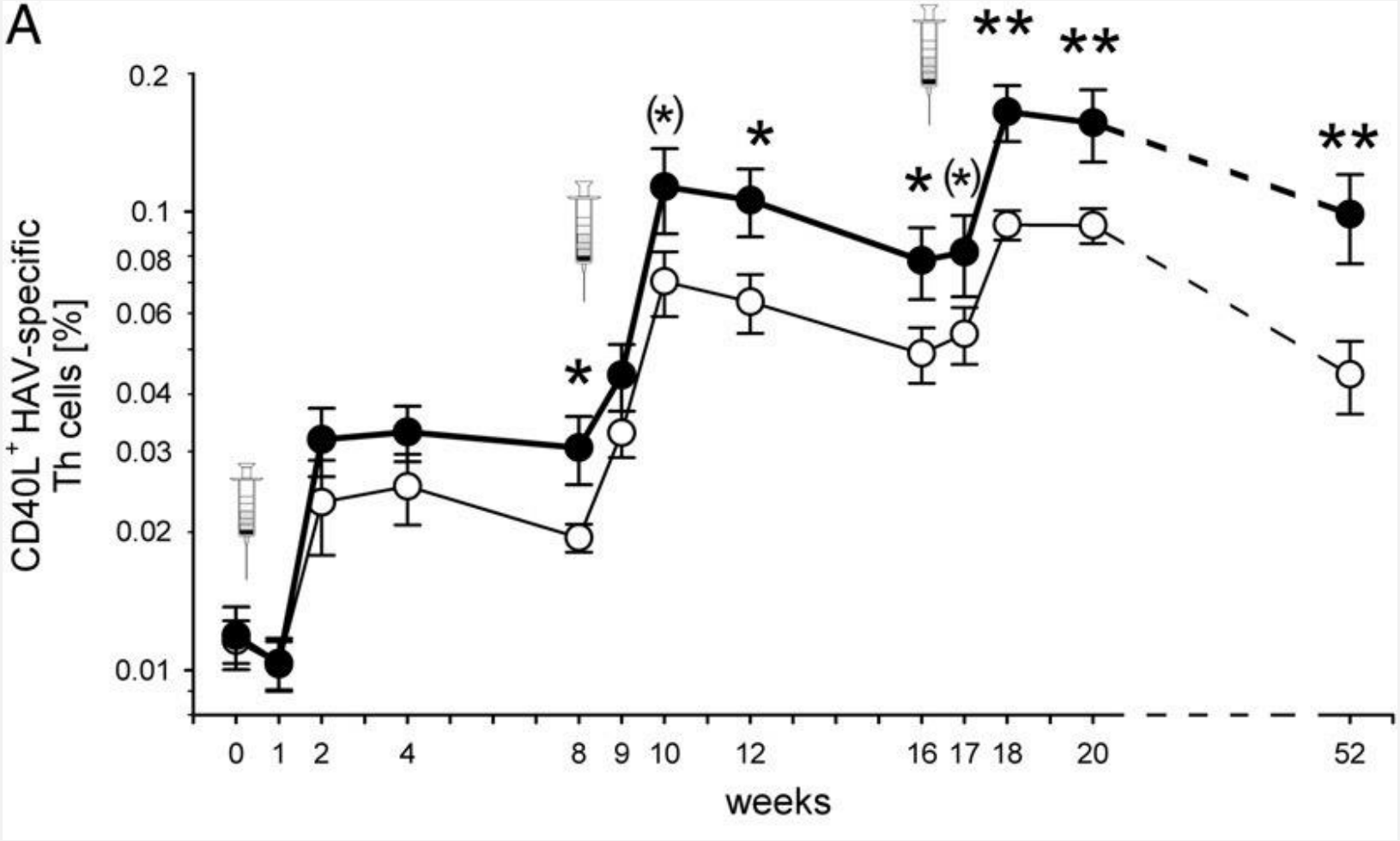
N Engl J Med 1996; 334:924-925



Increased Strokes

Sleep Med. 2016 Nov - Dec;27-28:20-24

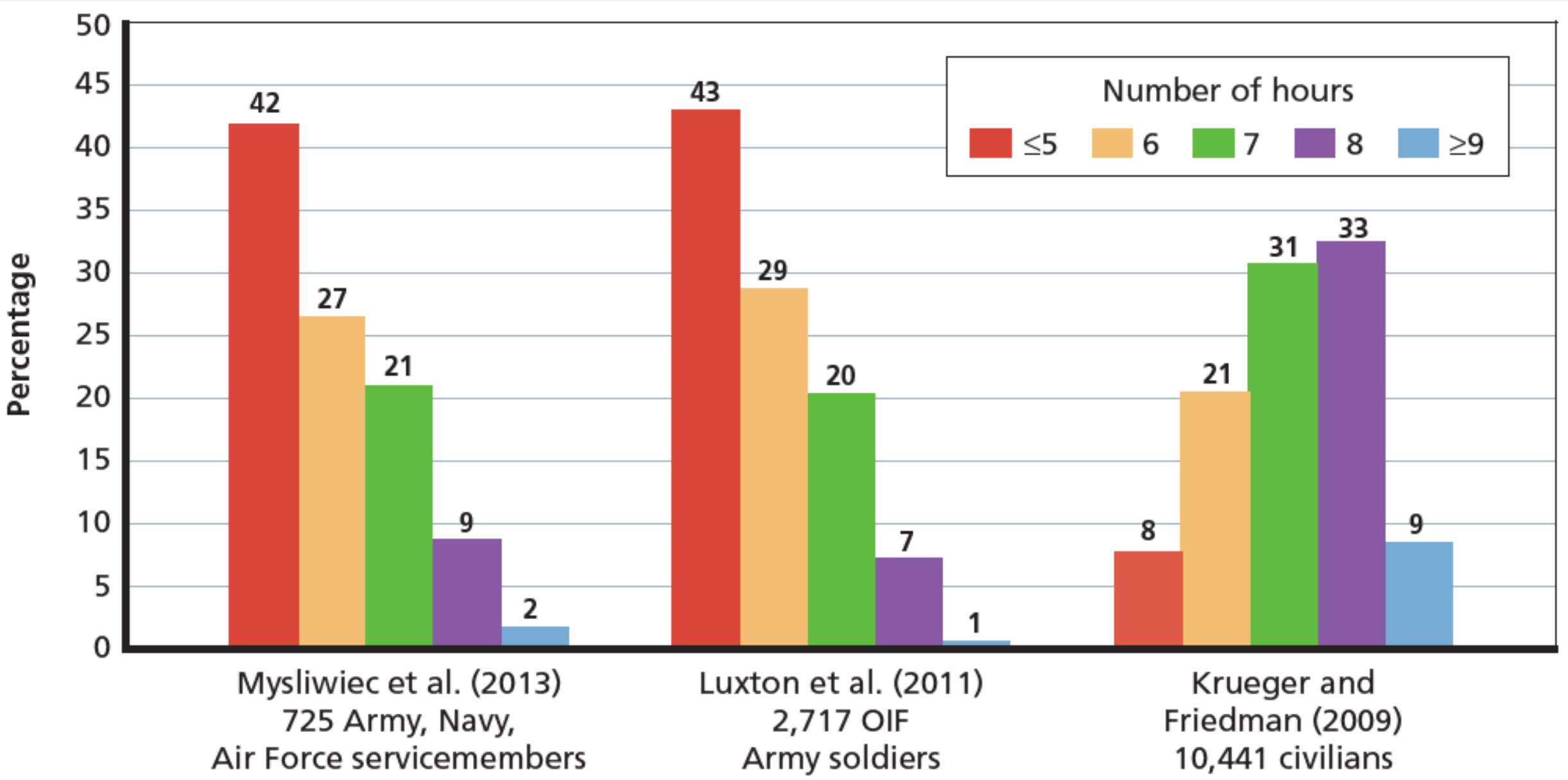
VACCINES ARE LESS EFFECTIVE WITHOUT GOOD SLEEP



The Journal of Immunology, 2011, 187: 283–290. Jan Born Lab

LIMBIC CENC

MILITARY SLEEP HABITS

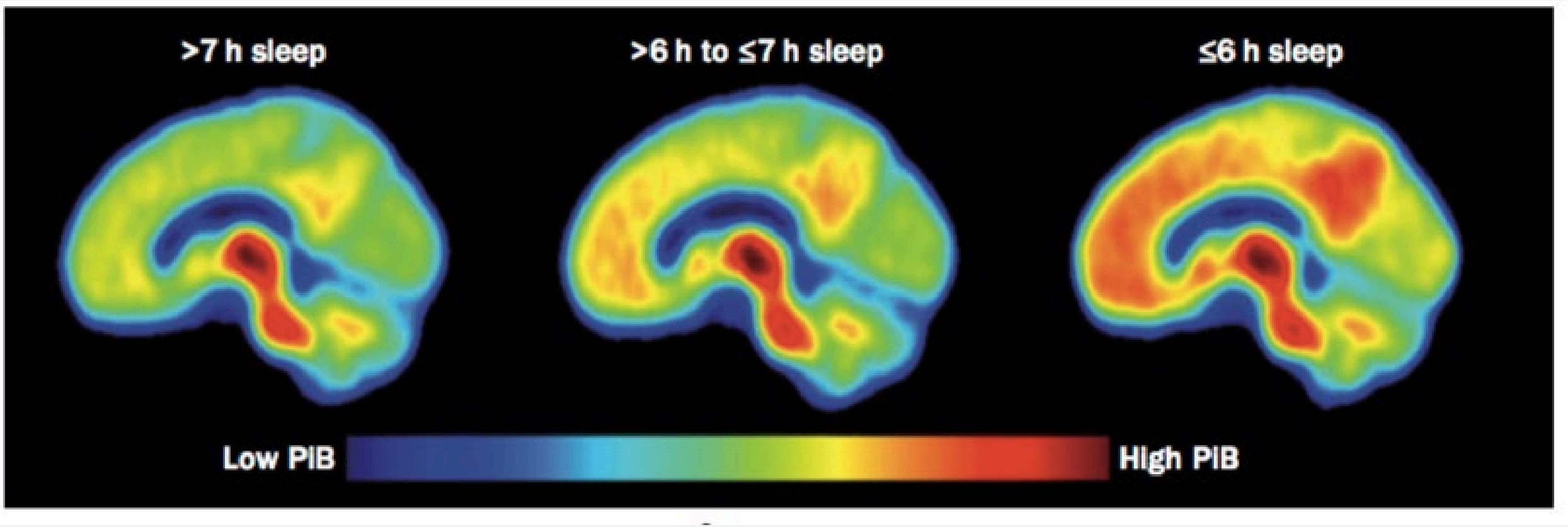


*In peace and war, the **lack of sleep** works like termites in a house: below the surface, gnawing quietly and unseen to produce gradual weakening which **can lead to sudden and unexpected collapse**.*

—Major General Aubrey Newman (Follow Me, 1981)

CONSEQUENCES OF SLEEP DYSFUNCTION

SLEEP CORRELATES WITH HUMAN AMYLOID BURDEN



Spira A et al. JAMA Neurol. 2013 Dec;70(12):1537-43.

nature COMMUNICATIONS

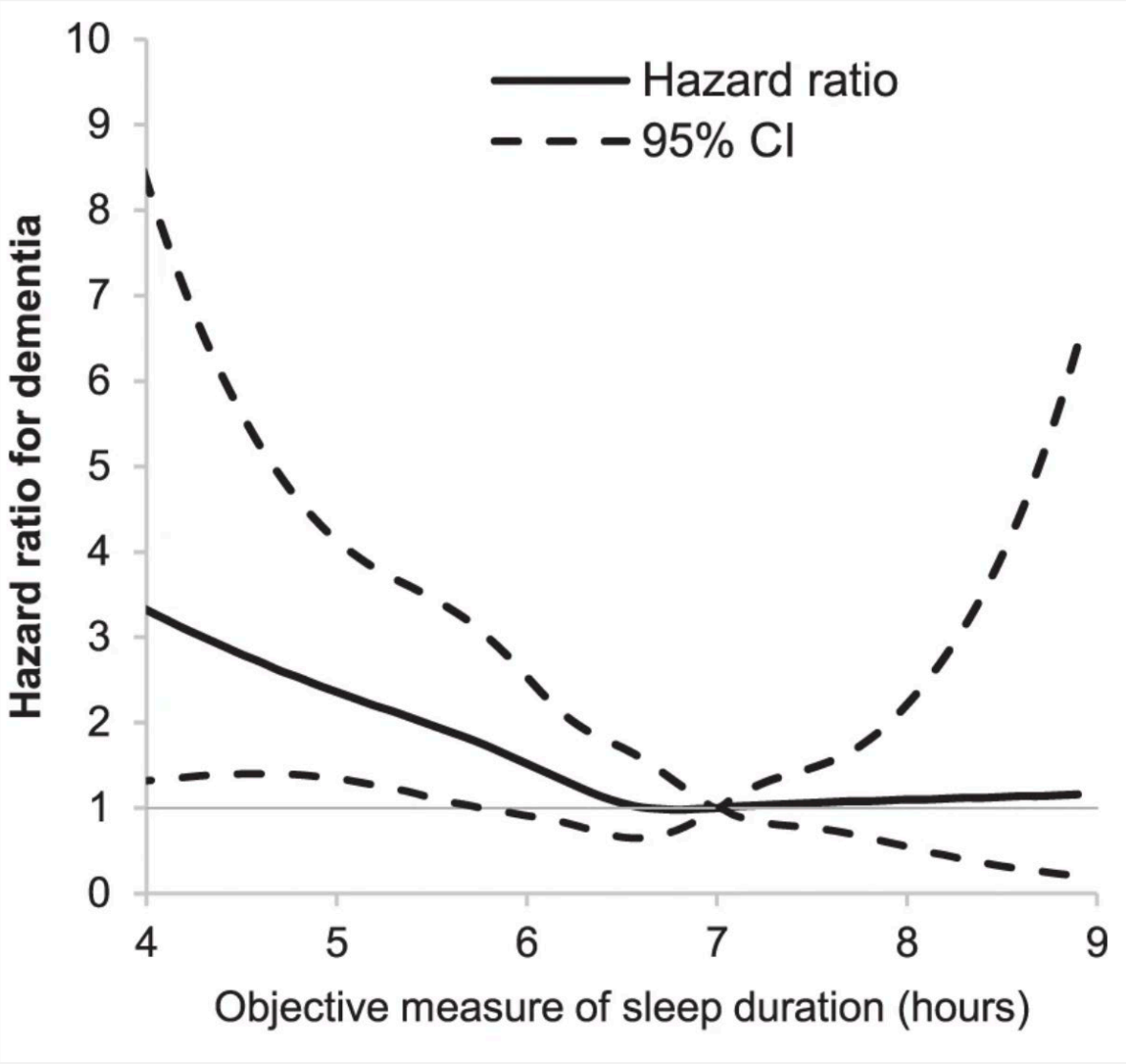
ARTICLE

https://doi.org/10.1038/s41467-021-22354-2 OPEN

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

Séverine Sabia[1,2✉], Aurore Fayosse[1], Julien Dumurgier[1,3], Vincent T. van Hees[4], Claire Paquet[3], Andrew Sommerlad[5,6], Mika Kivimäki[2,7], Aline Dugravot[1] & Archana Singh-Manoux[1,2]

- N=8000 (521 diagnosed with dementia)
- 25yr prospective study
- Ages 50-75



UNTREATED SLEEP DISORDER PATIENTS HAVE INCREASED RISK OF DEMENTIA

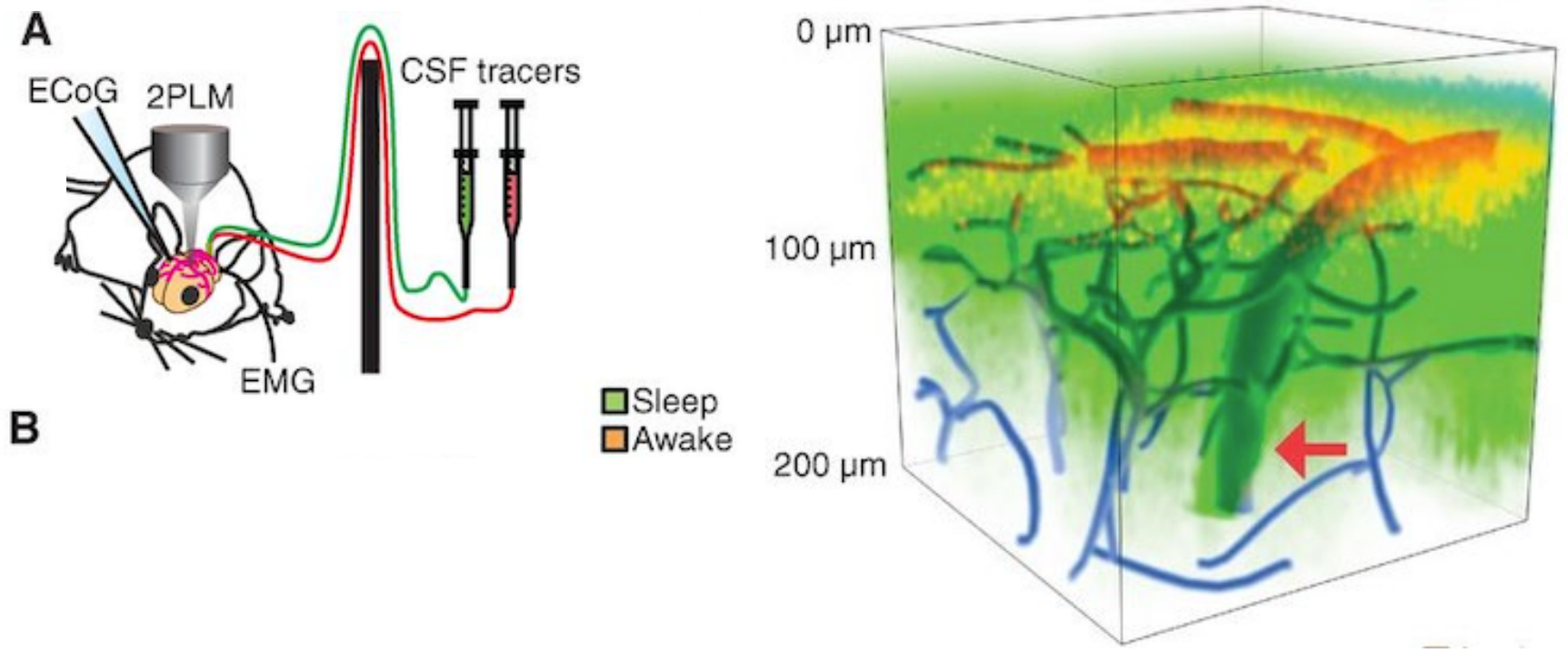
	Mild Cognitive Impairment or Dementia, No. (%) (n = 107)	OR (95% CI)	
		Unadjusted	Adjusted[a]
Hypoxia and Disordered Breathing Measures			
Oxygen desaturation index, events/h			
<15	46 (43.0)	1 [Reference]	1 [Reference]
≥15	60 (56.1)	1.67 (1.03-2.69)	1.71 (1.04-2.83)
Oxygen saturation <90%			
<1% of 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)
High (median: 16.4 [range, 7.0-66.8])	45 (42.1)	1.79 (1.01-3.20)	2.04 (1.10-3.78)

- Yaffe et al. JAMA 2011.

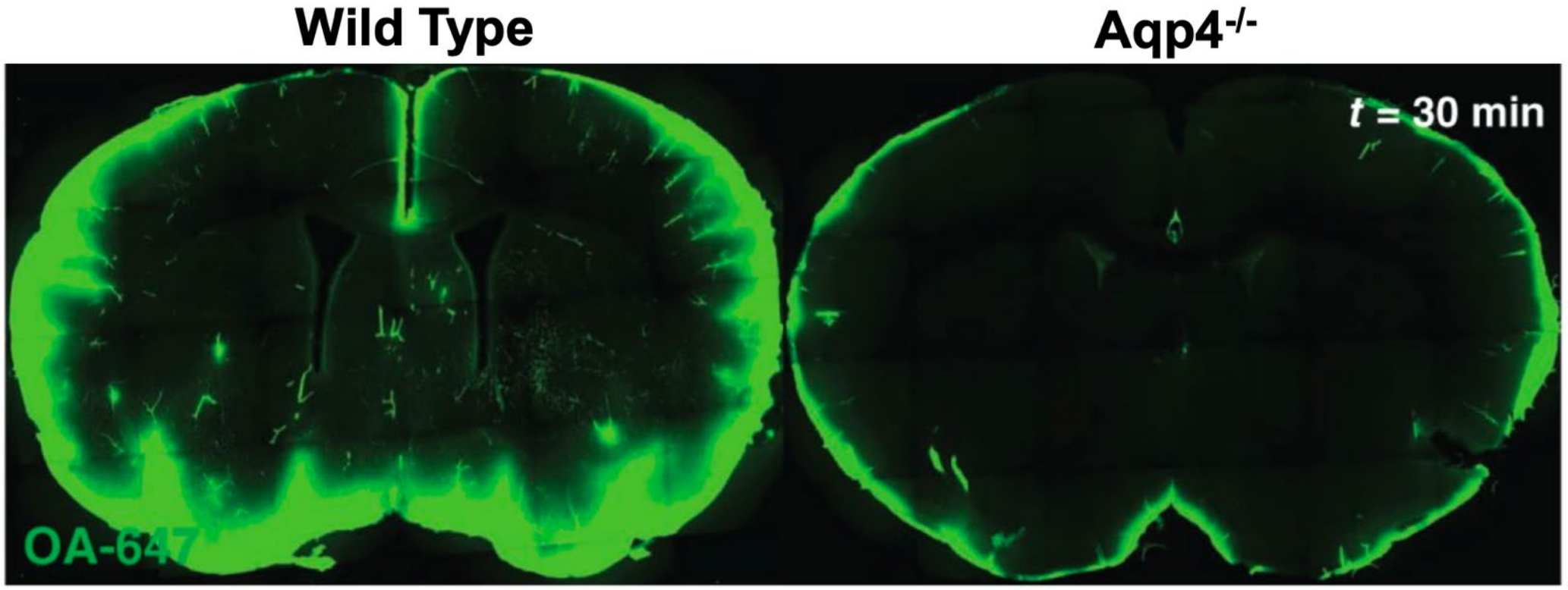
Science 363, 880–884 (2019) 18 October 2013.

Sleep Drives Metabolite Clearance from the Adult Brain

Lulu Xie,[1]* Hongyi Kang,[1]* Qiwu Xu,[1] Michael J. Chen,[1] Yonghong Liao,[1] Meenakshisundaram Thiyagarajan,[1] John O'Donnell,[1] Daniel J. Christensen,[1] Charles Nicholson,[2] Jeffrey J. Iliff,[1] Takahiro Takano,[1] Rashid Deane,[1] Maiken Nedergaard[1]†



Aqp4 knockout mouse has reduced CSF-ISF exchange



Iliff et al. *Sci Translat Med* 2012

JCI insight
Published by The American Society for Clinical Investigation | Founded 1908

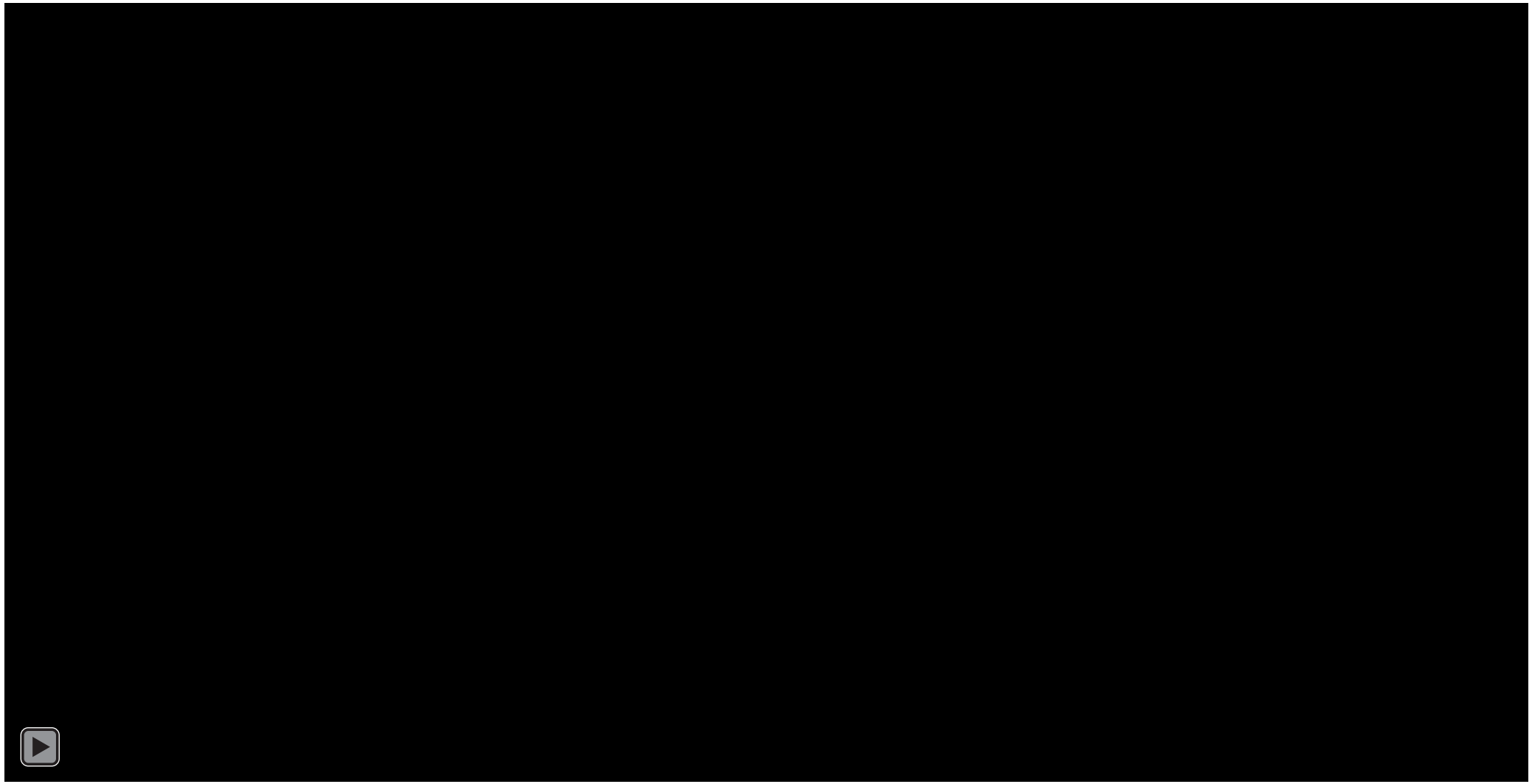
JCI Insight. 2018 Jul 12; 3(13): e121537.
Published online 2018 Jul 12. doi: 10.1172/jci.insight.121537

PMCID: PMC6124518
PMID: 29997300

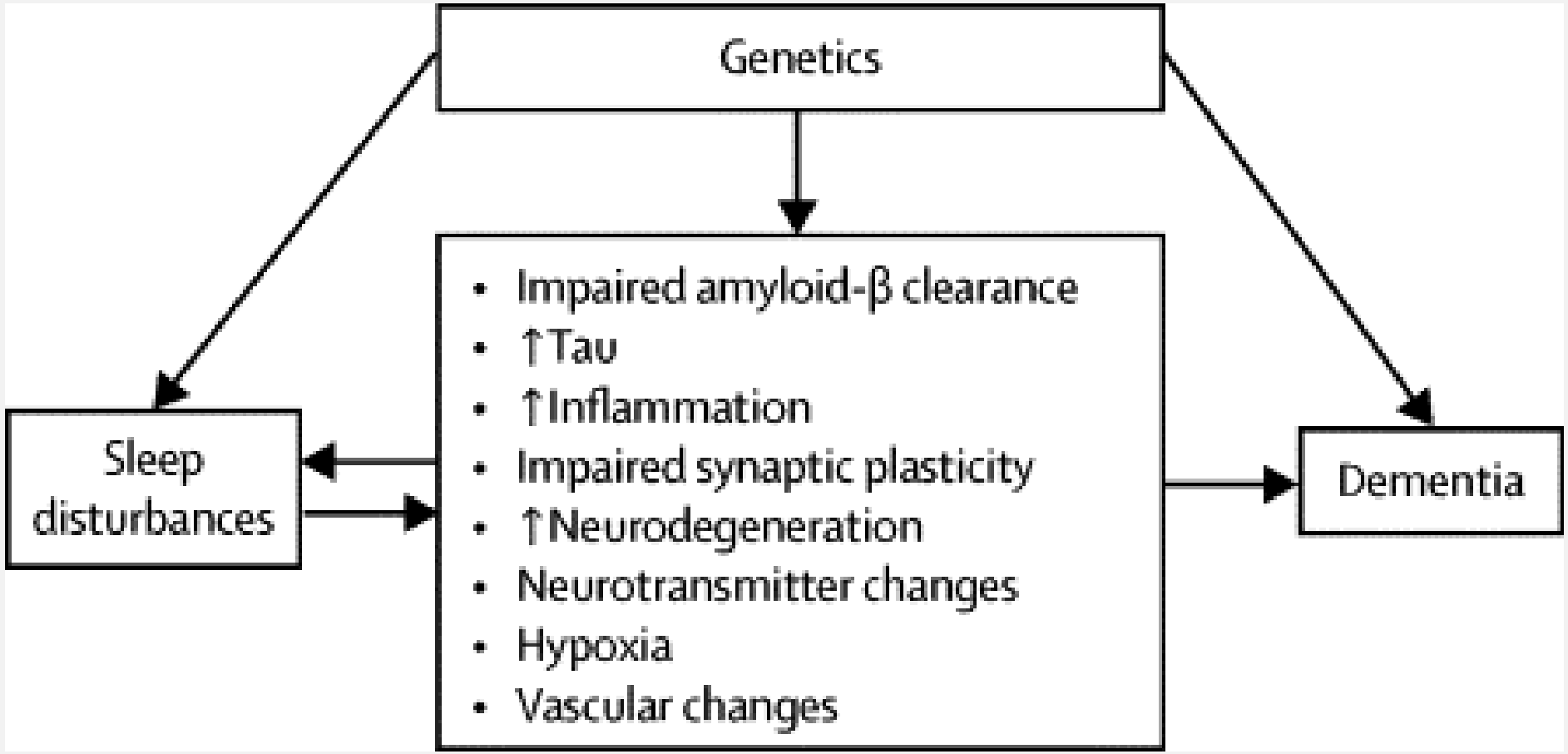
Brain-wide glymphatic enhancement and clearance in humans assessed with MRI

Geir Ringstad,[1,2] Lars M. Valnes,[3] Anders M. Dale,[4,5,6] Are H. Pripp,[7] Svein-Are S. Vatnehol,[8] Kyrre E. Emblem,[9] Kent-Andre Mardal,[3,10] and Per K. Eide[2,11]

Injecting gadolinium dye into the CSF is rarely permitted in the US
– *this was done in Norway*



SLEEP DYSFUNCTION CAUSING DEMENTIA IN A FEED-FORWARD CYCLE



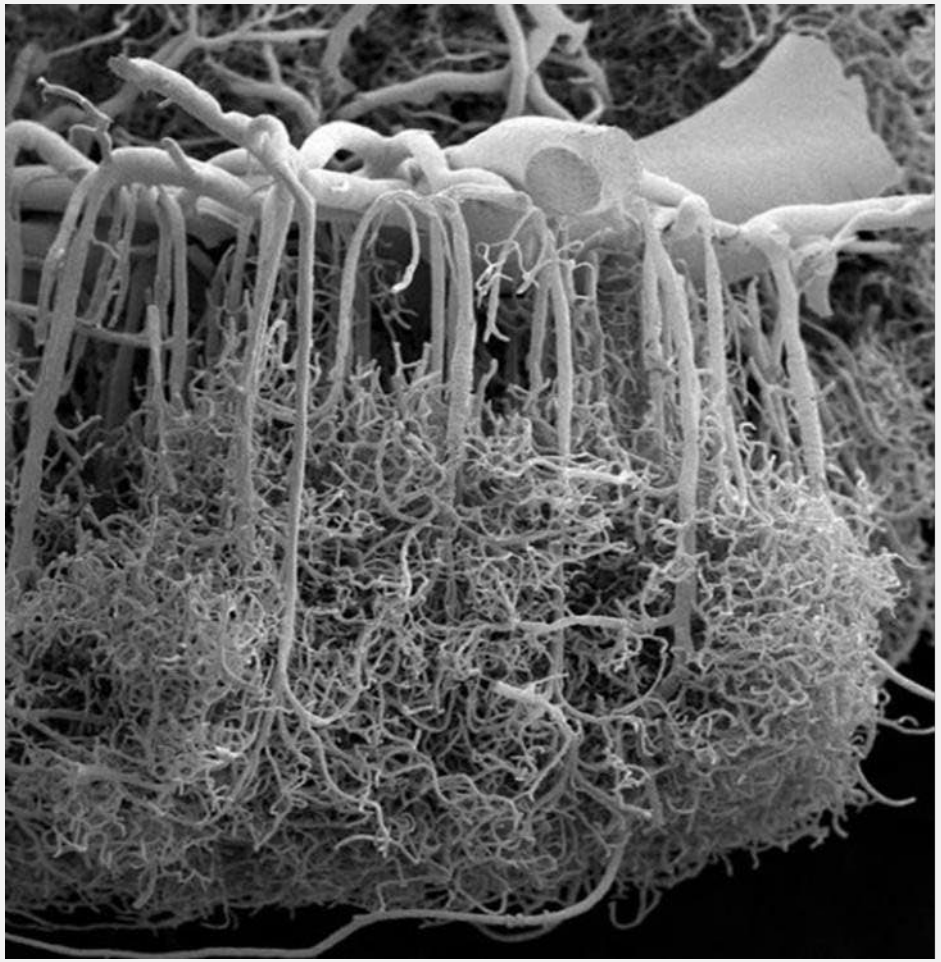
THE LANCET Neurology

Yaffe K et al. October, 2014

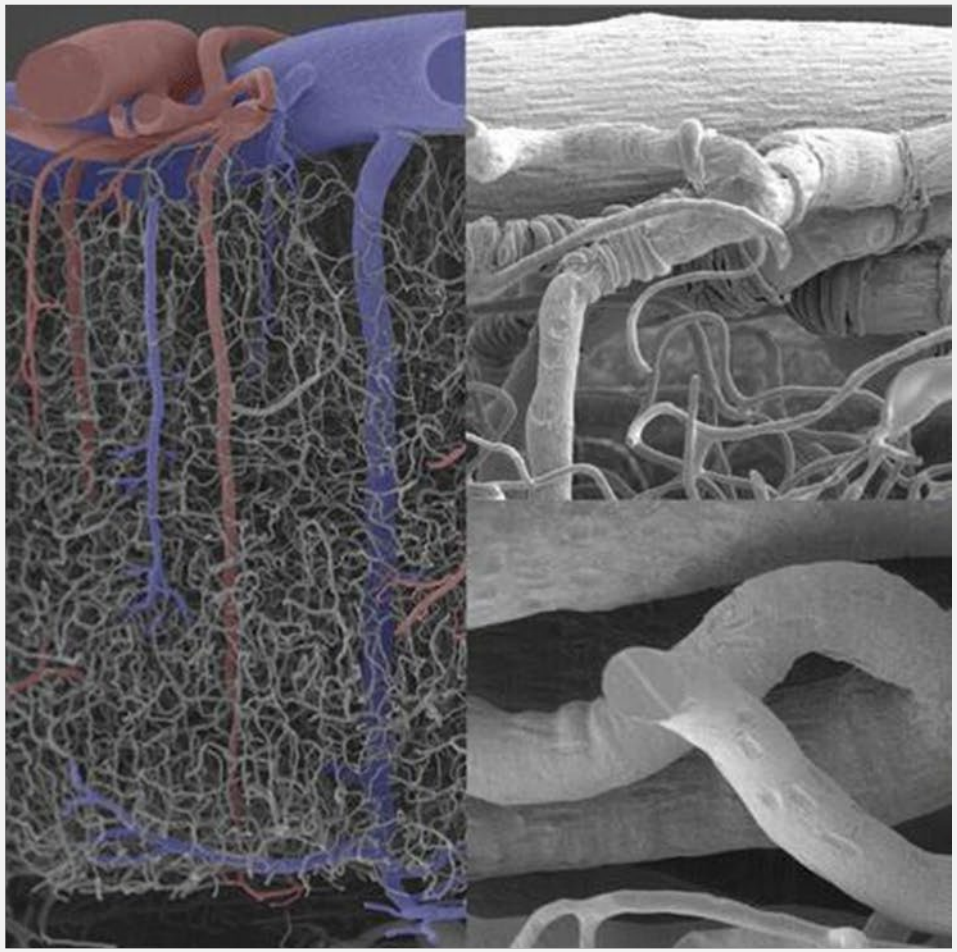
LIMBIC CENC

SLEEP DYSFUNCTION + TRAUMATIC BRAIN INJURY

ANATOMY OF NORMAL CEREBRAL MICROVASCULATURE

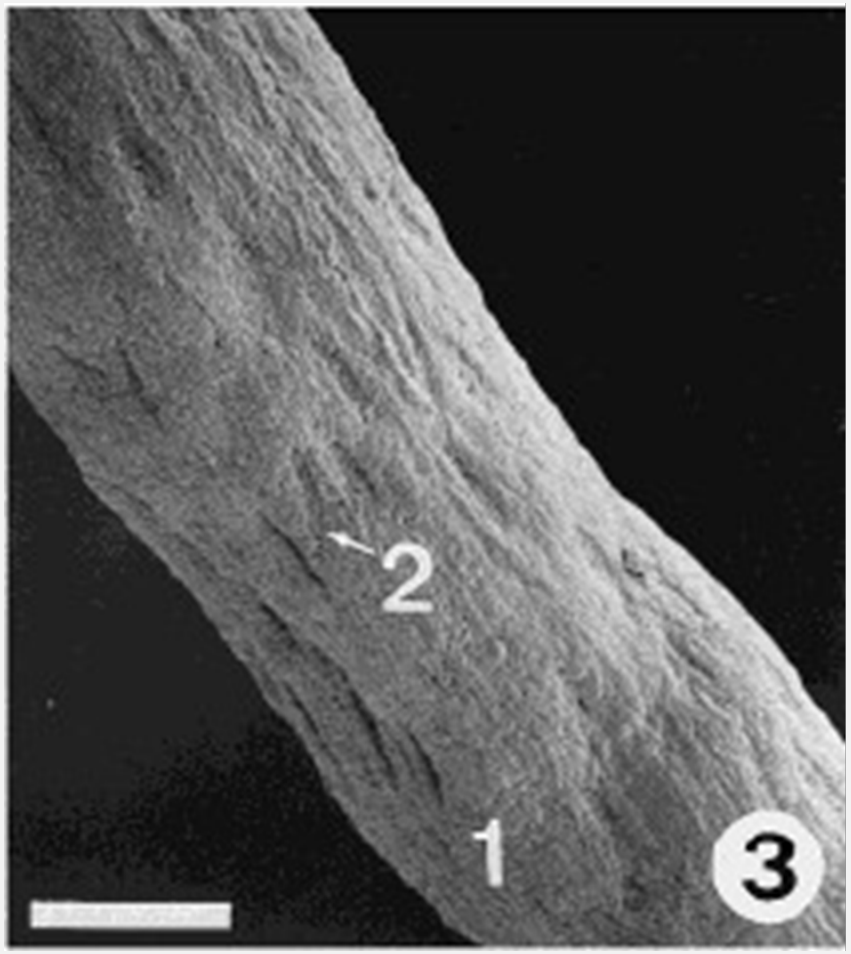


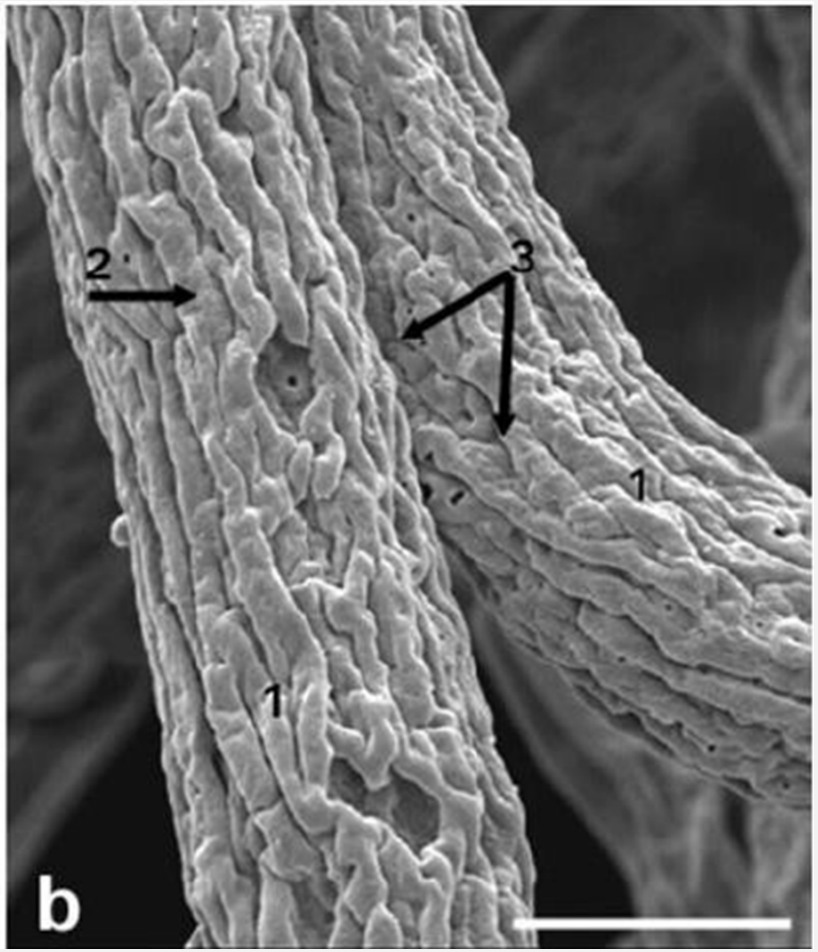
Reina de la Torre, et al Anat Record 1998;251:87-96



Weber et al Cereb Cortex 2008;18:2318

CEREBRAL MICROVASCULATURE IN TBI



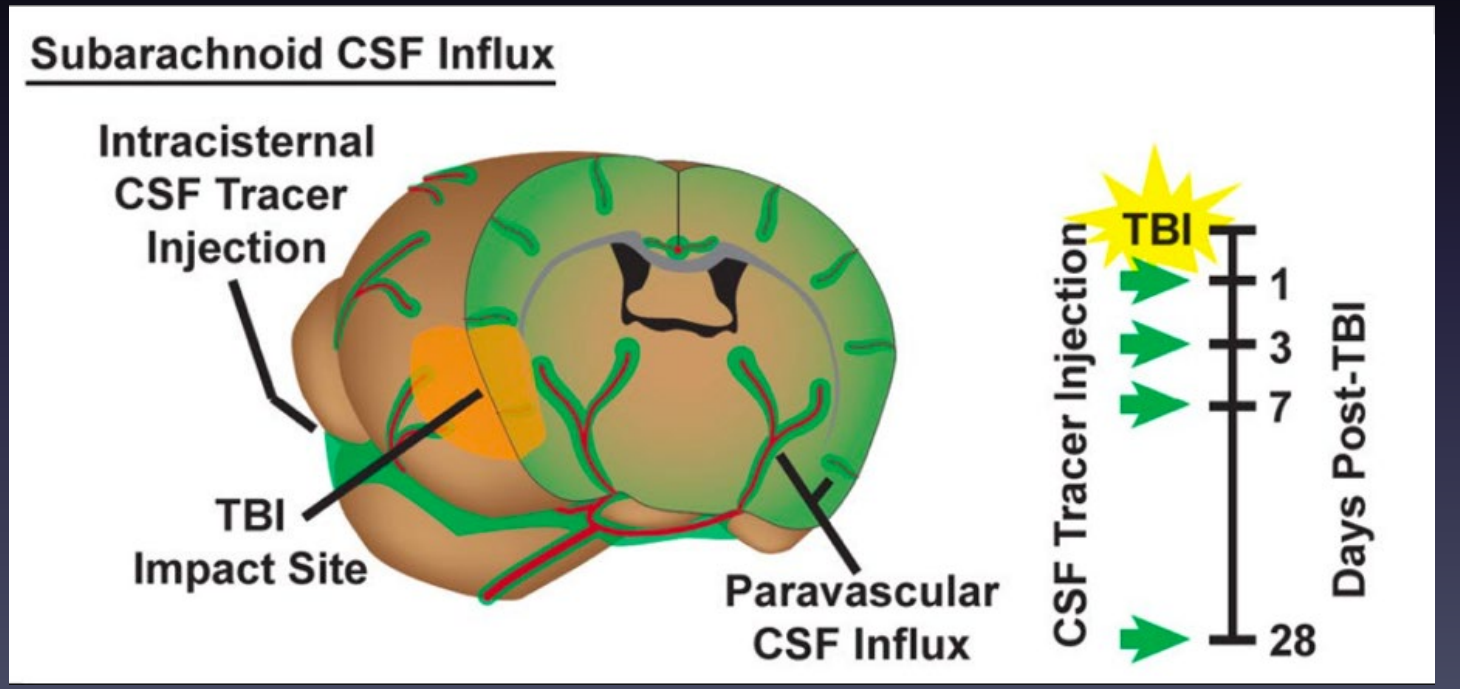


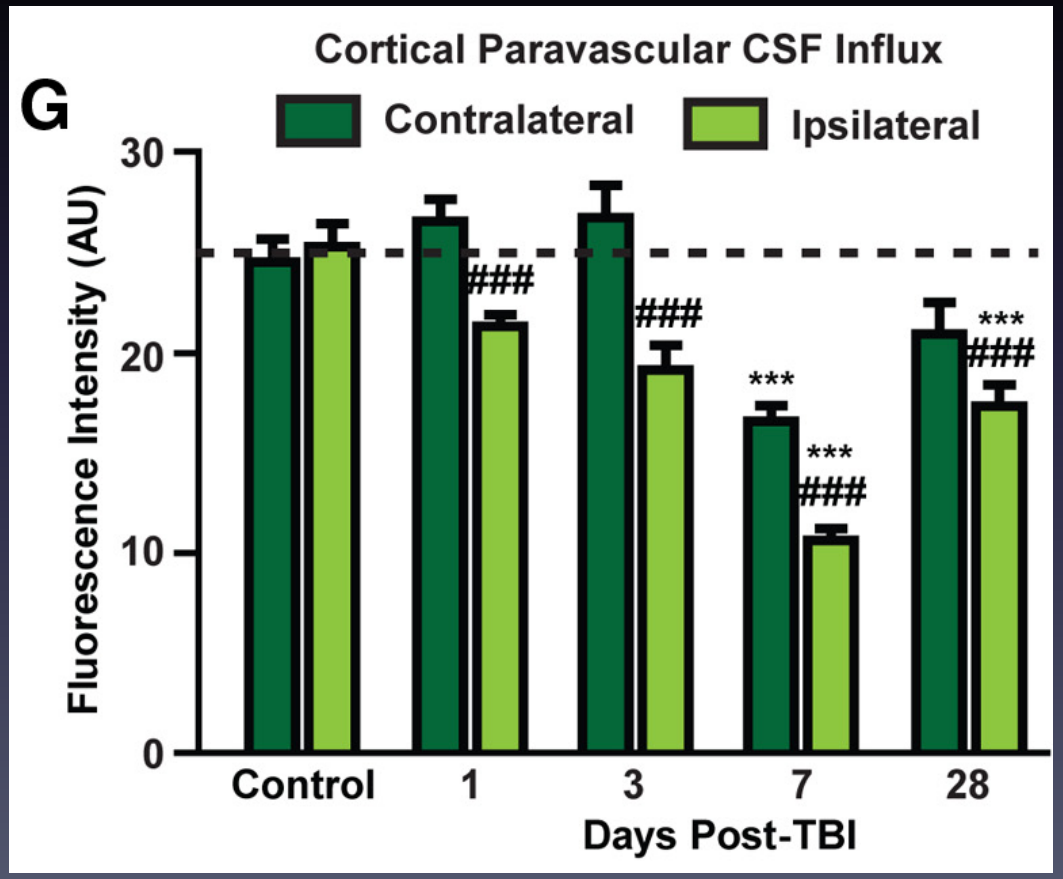
Rodriguez-Baeza, et al Anat Record 1998;252:176-184 Rodriguez-Baeza, et al Anat Record 2003;273A:583-593

J Neurosci 2014 34:16180-16193

Impairment of Glymphatic Pathway Function Promotes Tau Pathology after Traumatic Brain Injury

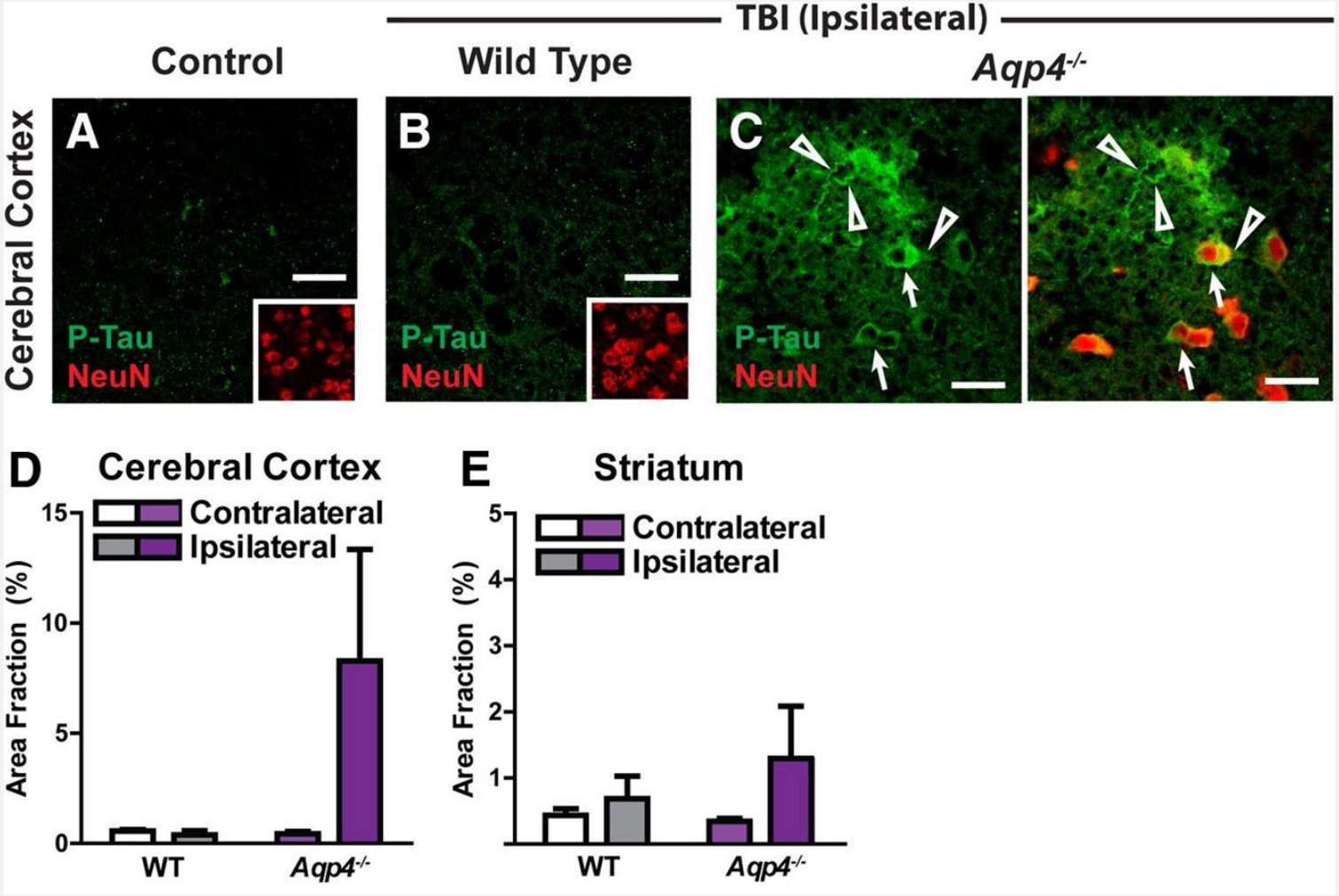
Jeffrey J. Iliff,[1,2,3] Michael J. Chen,[1] Benjamin A. Plog,[1] Douglas M. Zeppenfeld,[2,3] Melissa Soltero,[2] Lijun Yang,[1] Itender Singh,[1] Rashid Deane,[1] and Maiken Nedergaard[1]





NEURONAL P-TAU ACCUMULATION AFTER TBI

- WORSE in Aqp4 knockout mice



Iliff J J Neurosci 2014 34:16180-16193

MILD TRAUMATIC BRAIN INJURY IS ALSO A RISK FACTOR FOR **SLEEP DISORDERS**

~50% of concussion patients develop sleep disorders

- Insomnia (20-50%)
- Sleep Apnea (25%)
- Hypersomnia (25%)
- Narcolepsy (5%)

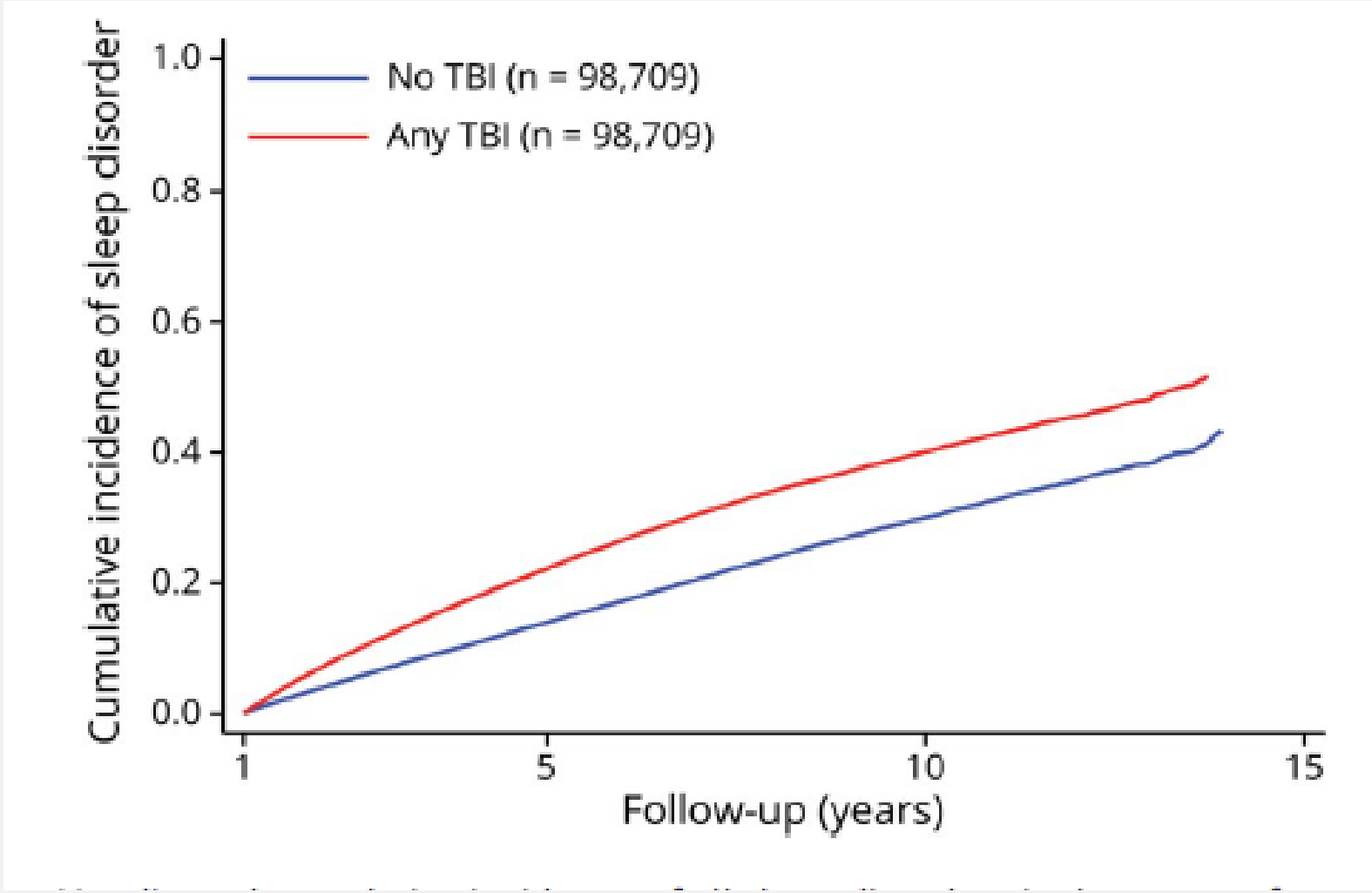
Neurology®

Traumatic Brain Injury and Incidence Risk of Sleep Disorders in Nearly 200,000 US Veterans

Yue Leng, MD, PhD, Amy L. Byers, PhD, Deborah E. Barnes, PhD, Carrie B. Peltz, PhD, Yixia Li, MPH, and Kristine Yaffe, MD

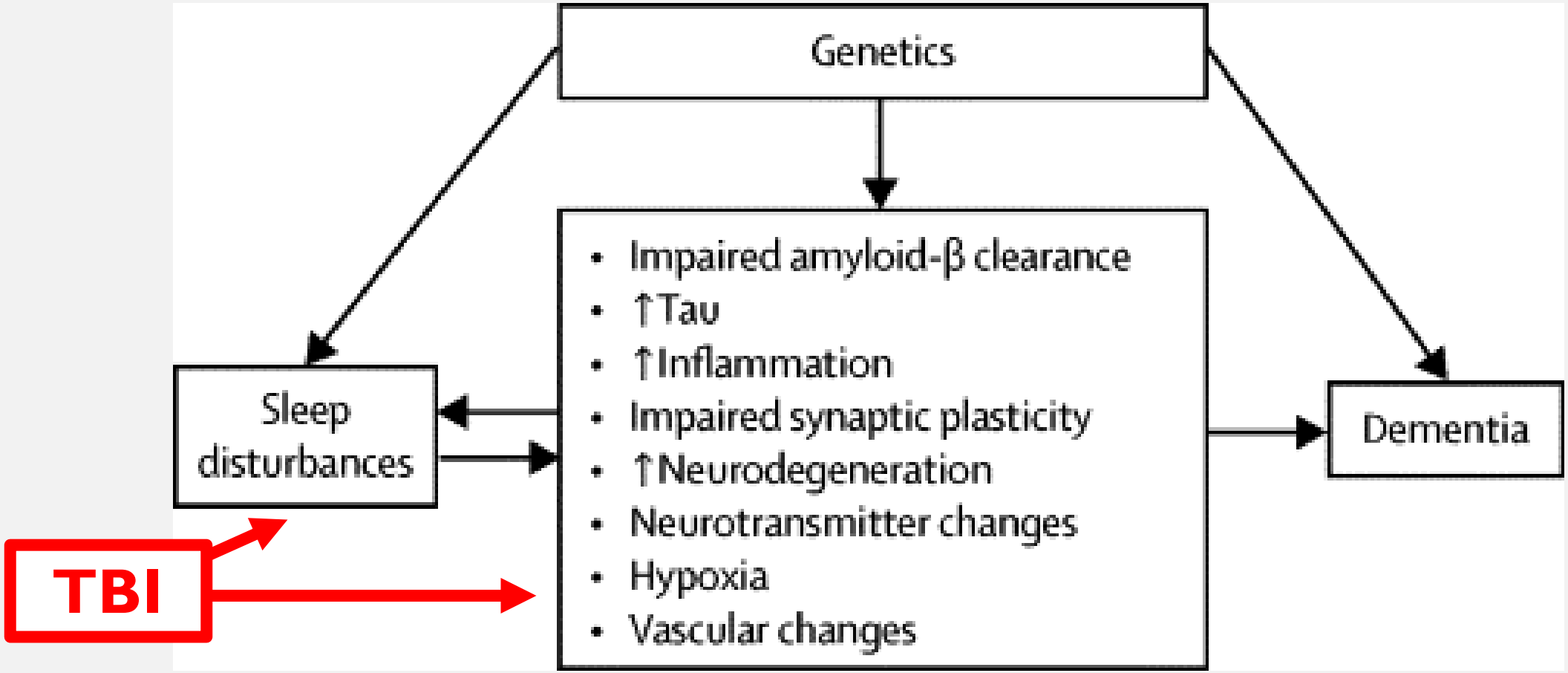
Correspondence
Dr. Leng

- N =197,418 Veterans
- NO sleep disorder at baseline
- 5 yr follow up
- mTBI assoc. not affected by PTSD dx
- Adj. for:
  - Demographics
  - Education
  - Income
  - Medical and psychiatric dx
- Hazard ratios TBI vs no TBI:
  - Insomnia 1.5
  - Hypersomnia 1.5
  - Sleep apnea 1.28
  - Sleep-movement disorder 1.33



Leng et al. Neurology 2021

LIMBIC CENC SLEEP DISORDERS + TBI = FEED FORWARD CYCLE FOR DEMENTIA

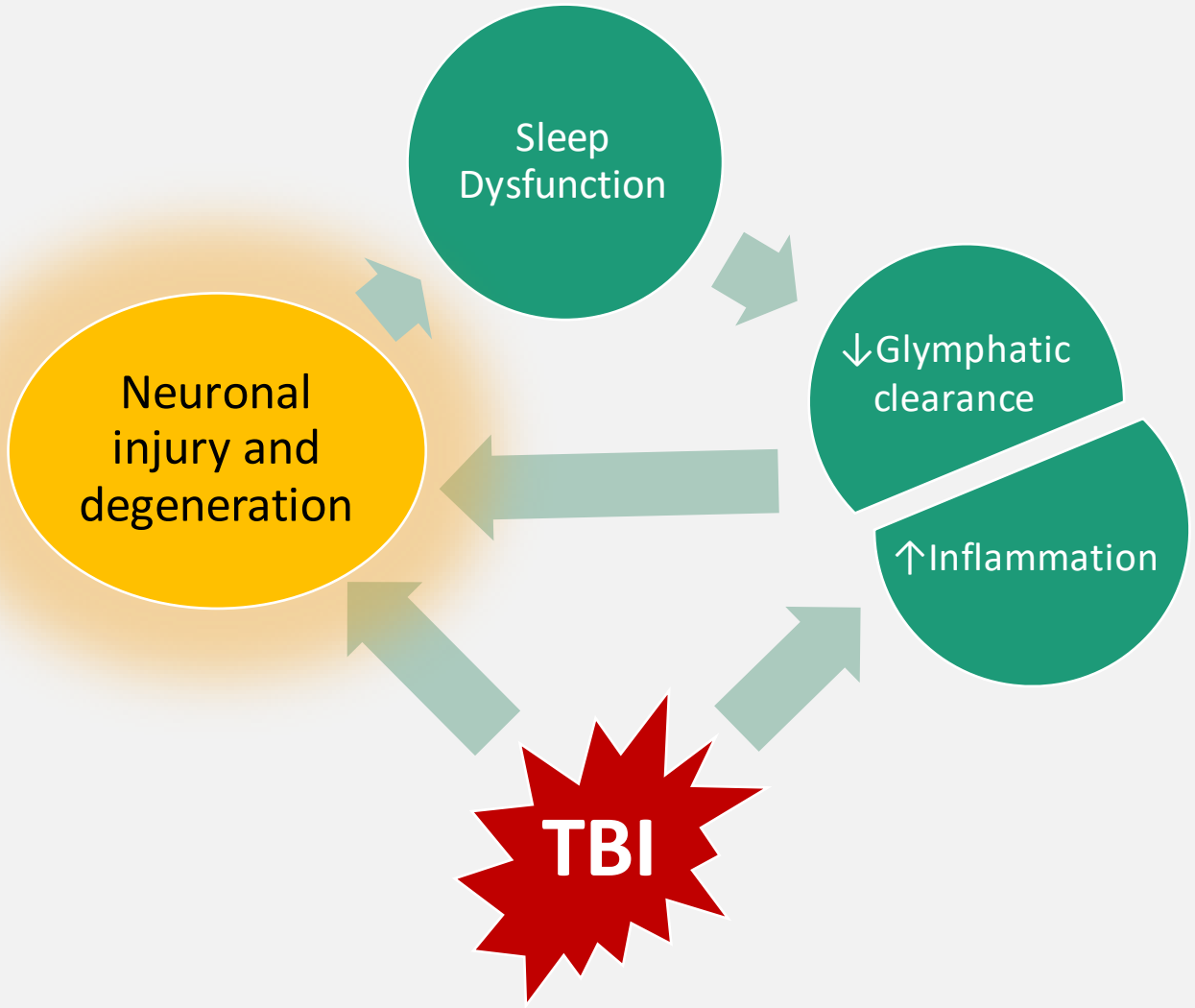


THE LANCET Neurology

Modified from Yaffee K et al. October, 2014

Hypothesis

DYSFUNCTIONAL SLEEP AFTER TBI PROMOTES NEURODEGENERATION



Methods

1) **COHORT:** derived from CENC - Chronic Effects of Neurotrauma Consortium

- DoD and VA collaboration
- Multi-site, combat-deployed active duty and veterans with/without mild (only) TBI
- Longitudinal cohort with blood, MRI imaging, and interviews/questionnaires

2) **OUTCOMES:**

- Poor sleepers: PSQI ≥ 10 (Pittsburgh sleep quality index)
- Categorical Fluency and Stop-Go testing (Executive function)
- STOP-BANG score assesses risk of having obstructive sleep apnea. "High Risk" is >3
- Plasma Neurodegenerative biomarkers: (Single Molecule Array – SIMOA)
  - Amyloid beta (Aβ42)
  - Neurofilament light (NfL)
  - Tau

Cohort

- Average 10.1 (8.6-11.6) years from index combat-deployed mTBI

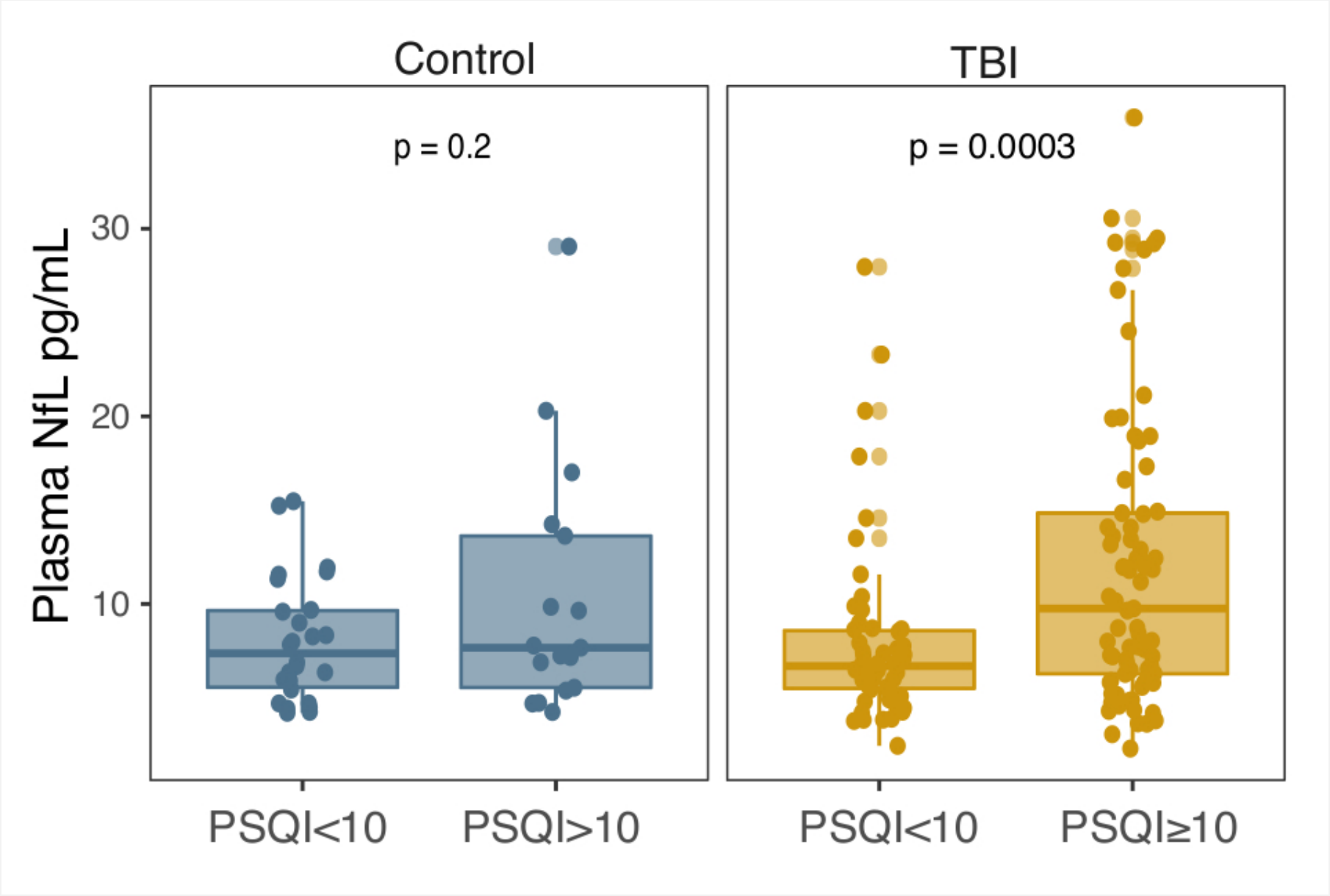
Characteristics (SD)	Controls (N=44)	TBI (N=142)	*p*=
Age	40.0 (11.5)	40.2 (10.7)	NS
% Males	84.0 %	87.1%	NS
% White	75.0%	70.5%	NS
BMI	29.2 (4.7)	30.6 (5.6)	NS
Avg. hours of sleep	5.9 (1.4)	5.4 (1.7)	NS
STOP-BANG	2.8 (1.5)	3.4 (1.8)	NS
PSQI	**8.3 (5.6)**	**10.7 (4.8)**	**0.015***
NSI	**17.0 (15.3)**	**30.3 (16.4)**	**<0.00001*****
PCL-5	**18.5 (17.8)**	**31.0(19.8)**	**<0.001****
Categorical Fluency Test	19.4 (5.7)	19.2 (4.9)	NS
Stop-Go Test	31.2 (1.7)	30.5 (2.7)	NS

Results

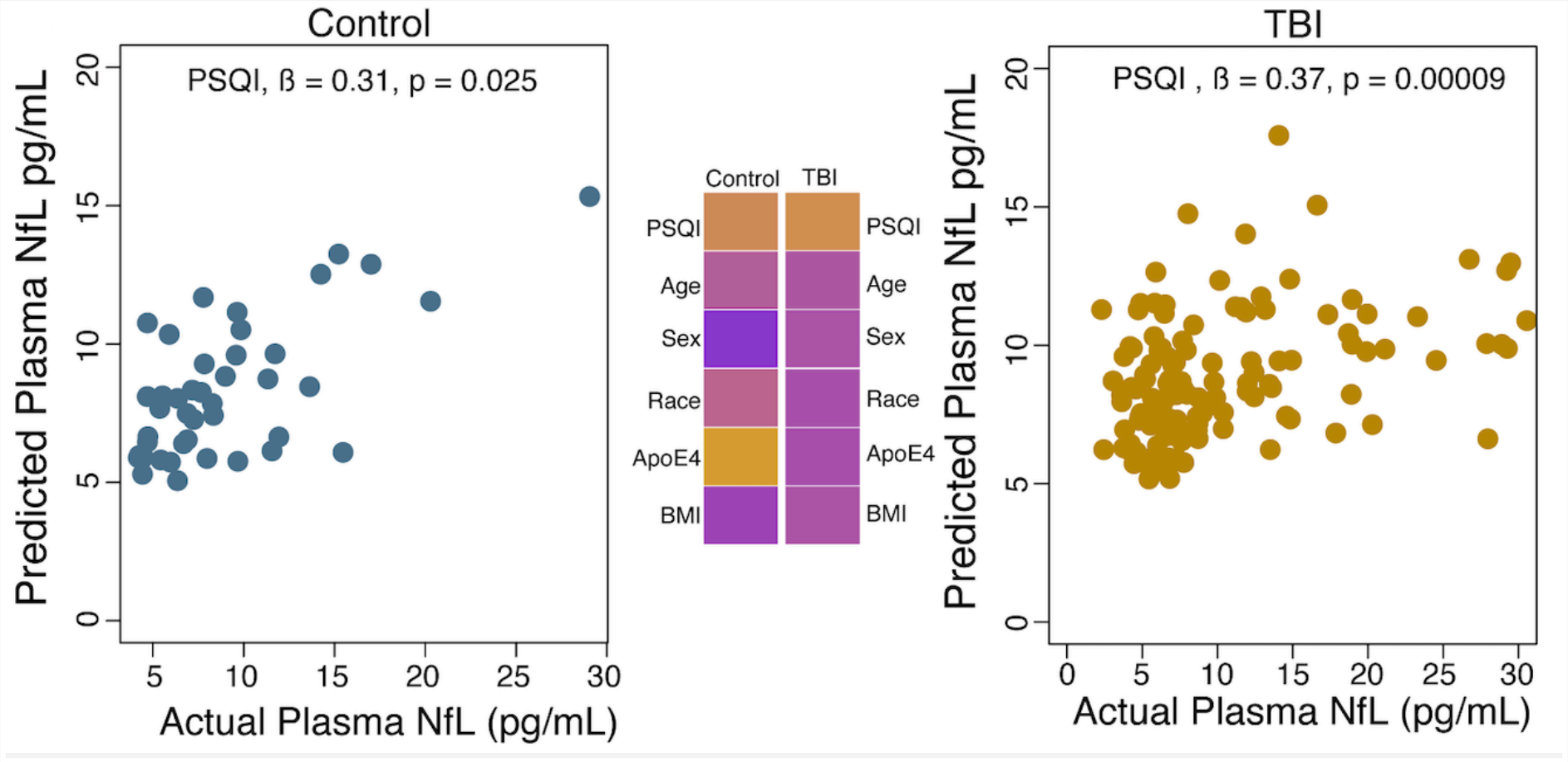
Biomarker pg/mL (SD)	Controls (N=44)	TBI (N=142)	*p*=
Amyloid β-42	6.5 (2.4)	6.9 (2.7)	NS
Tau	2.1 (1.1)	2.4 (1.4)	NS
Neurofilament light	8.9 (5.0)	10.3 (7.3)	NS

LIMBIC CENC

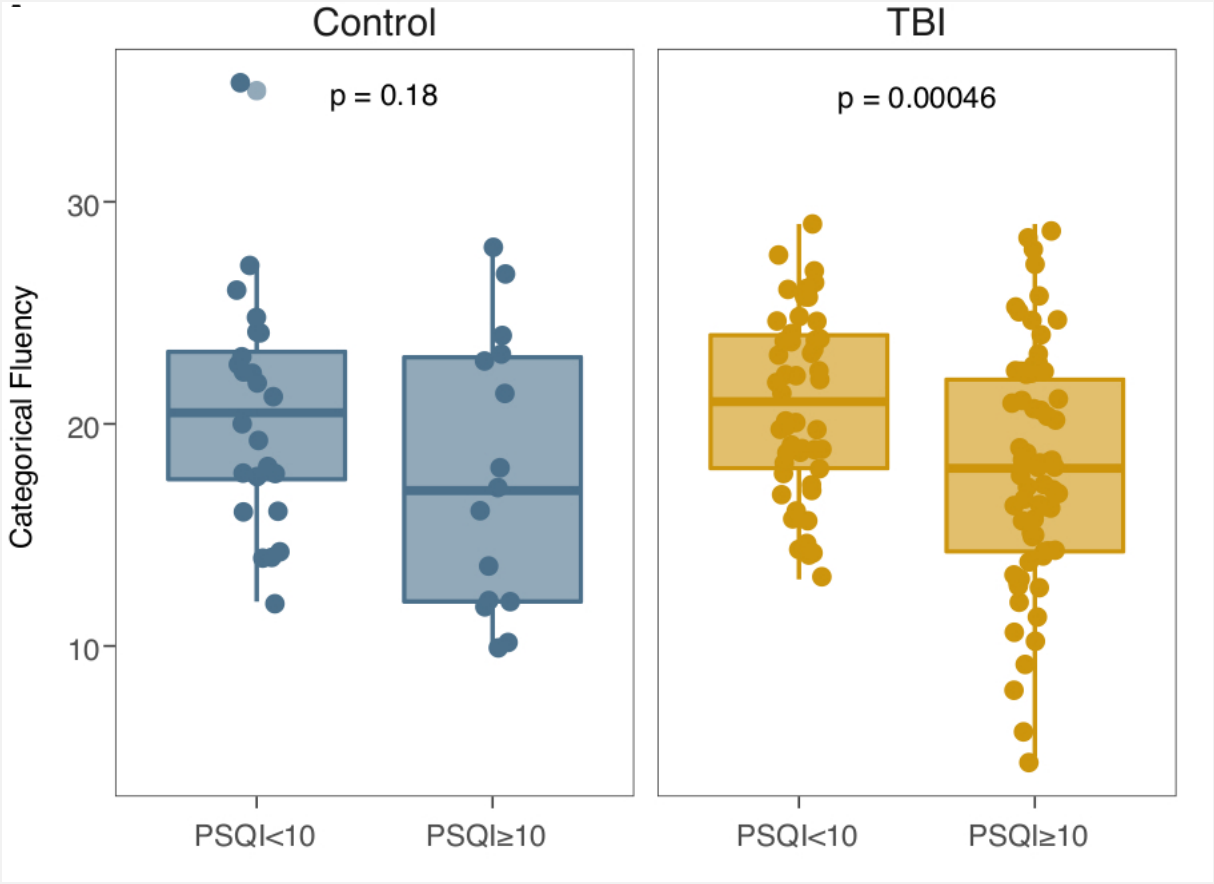
NEURO-FILAMENT LIGHT IS ELEVATED IN POOR SLEEPERS WITH TBI



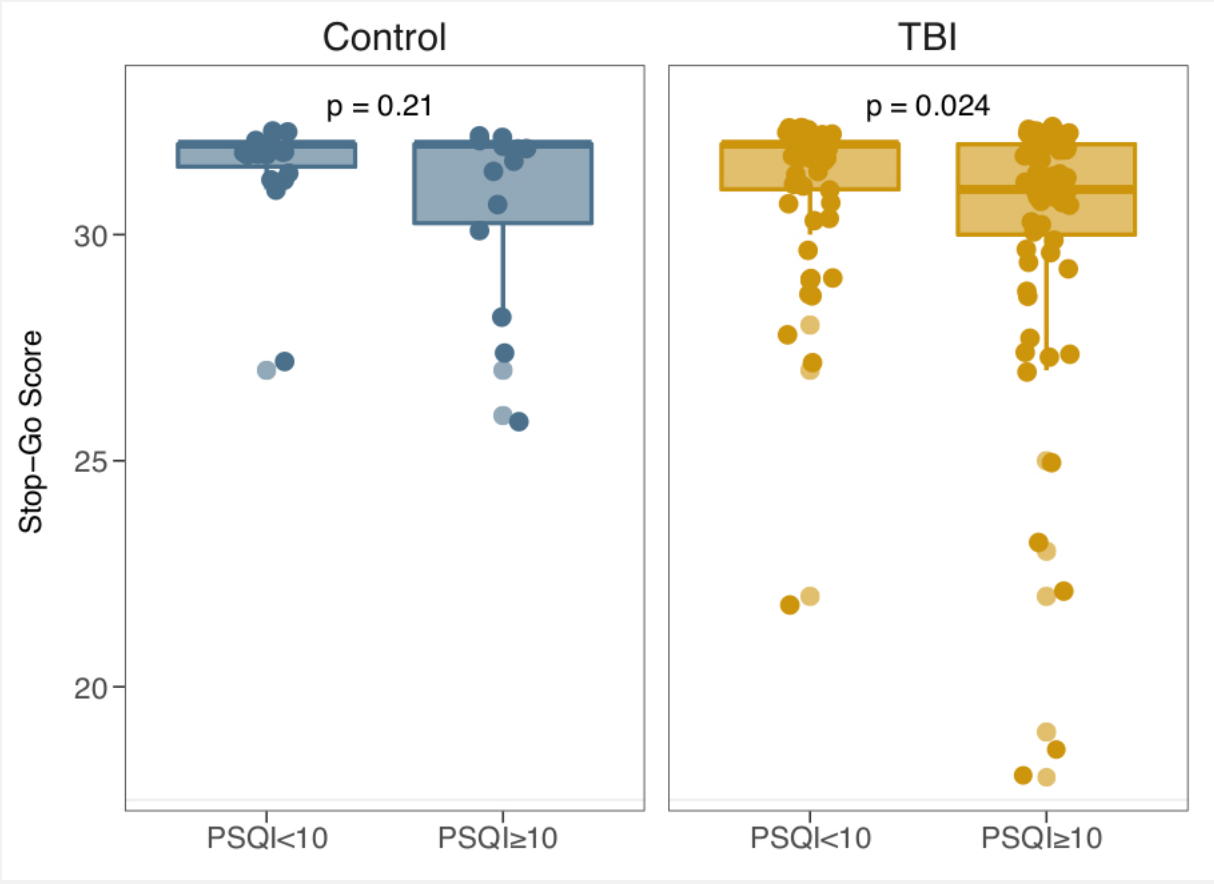
SLEEP QUALITY IS STRONGEST PREDICTOR OF NFL IN CHRONIC TBI, NOT CONTROLS



EXECUTIVE FUNCTION PERFORMANCE WORSE IN POOR SLEEPERS + TBI

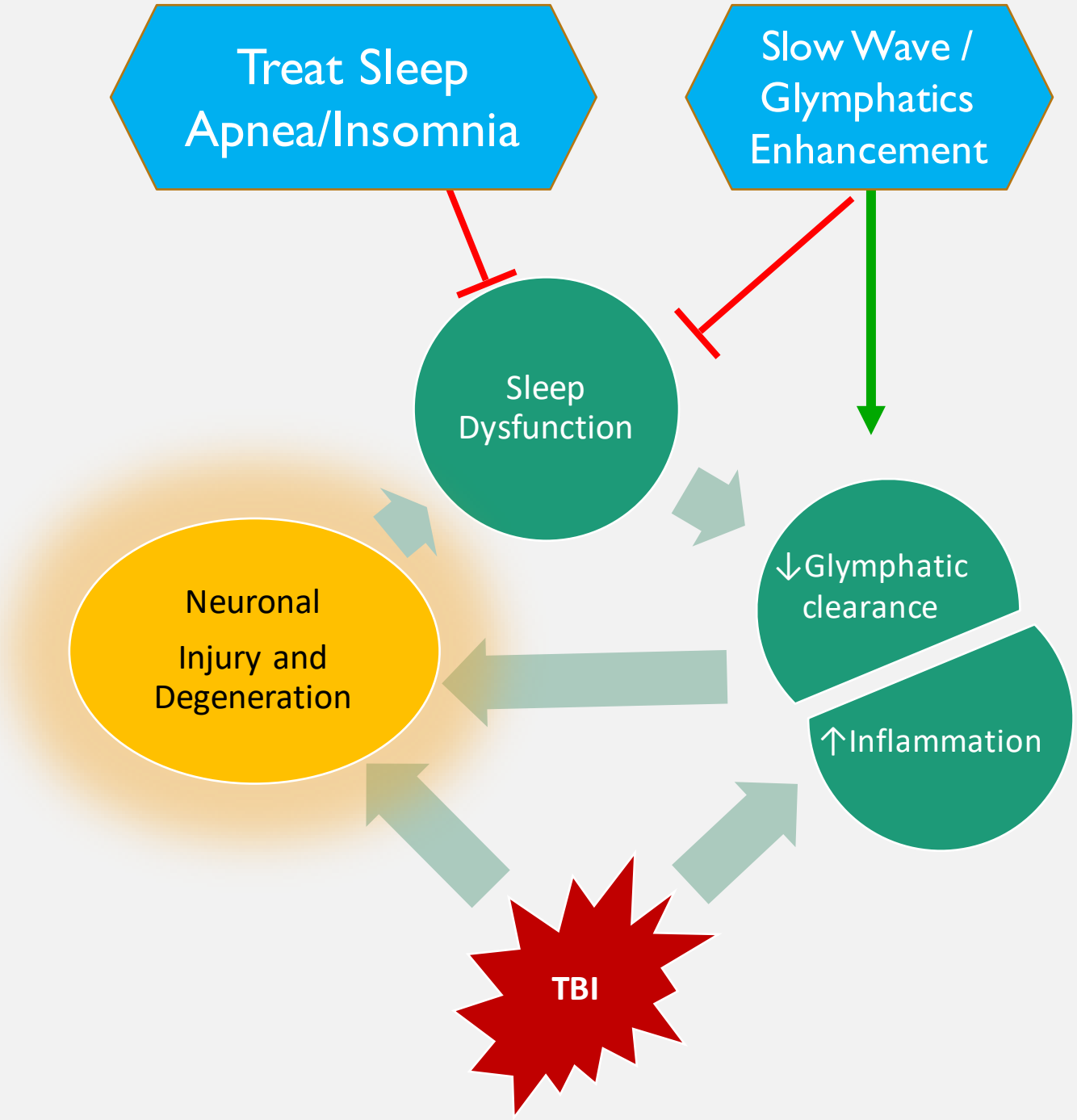


Categorical Fluency Test



Stop – Go Test

SLEEP RELATED INTERVENTIONS MAY REDUCE NEURODEGENERATION



LIMBIC CENC LIMITATIONS

- Laboratory results:
  - Plasma p-tau not measurable
- Small overall N, though largest to date
- Cross-sectional analysis
  - Large variation of time since initial, most recent and index TBI
  - Large variation in time between injuries
  - Large variation in TBI mechanisms
- **Cohort overall cognitively "normal"**

CONCLUSIONS

SUMMARY OF FINDINGS:

1) Poor sleepers with remote mTBI have elevated biomarkers of neurodegeneration
2) Poor sleepers lower scores on executive function testing
3) Sleep quality correlates with plasma NfL and tau, not amyloid

IMPLICATIONS: (if confirmed in a larger, prospective study)

1) NfL could serve as a prognostic biomarker of TBI-related dementia
2) Dysfunctional glymphatic clearance (TBI / sleep dysfunction) could mediate TBI related dementia
3) **Sleep/glymphatic dysfunction: A novel TBI treatment/preventative target?**

FUTURE DIRECTIONS

- Test larger LIMBIC-CENC cohort (up to additional 1,500 samples) cross-section
  - biomarkers of neurodegenerative disorders compared to sleep and cognitive function
- Collect longitudinal data (candidate biomarkers/neurocognitive outcomes) in a population in an aged post-TBI cognitive decline
- Correlate longitudinally assessed candidate diagnostic and prognostic biomarkers with sleep disorder diagnoses, cognitive function and glymphatic functional imaging

ARMY

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.

ACKNOWLEDGEMENTS

BLOOD BIOMARKERS TEAM

- J. Kent Werner, Jr. MD PhD (USU, WRNMMC)
- Josephine Pucci, MS (USU)
- Jessica Gill, PhD (NIH)
- Vivian Guedes, PhD (NIH)
- Sara Mithani, PhD (NIH)
- Chen Lai, PhD (NIH)
- Pashtun Shahim, MD PhD (NIH)
- Risa Nakase-Richardson, PhD (DVBIC, VA, USF)
- Ramon Diaz-Arrastia, MD PhD (U Penn)
- Kimbra Kenney, MD (USU, WRNMMC)

ACKNOWLEDGEMENTS

We thank the military Service members and Veterans who participated in this study;

LIMBIC-CENC Leadership: Col. Sidney Hinds (Co-PI), Kristine Yaffe MD (Co-PI), David Cifu MD (Consortium PI)

The CENC Observational Study Site Pis/co-PIs also include: Heather Belanger PhD (Tampa), Carlos Jaramillo MD (SanAntonio), Ajit Pai MD (Richmond), Melissa Guerra MD (Fort Belvoir), Randall Scheibel PhD (Houston), Terri Pogoda PhD (Boston), Scott Sponheim PhD (Minneapolis), Kathleen Carlson PhD (Portland), William Walker MD (Richmond).

We also acknowledge the efforts of the entire CENC Observational Study Leadership Working Group and Core Team members also include: Justin Alicea, Jessica Berumen, Cody Blankenship, Jennifer Boyce, Linda Brunson, Katrina Burson, Julia Christensen, Margaret Clarke, Doreen Collins, Sureyya Dikmen, Esra Doud, Connie Duncan, Stephanie Edmunds, Robyn Endsley, Elizabeth Fogleman, Laura M. Franke, Katelyn Gormley, Brenda Hair, Jim Henry, Nancy Hsu, Cheryl Ford-Smith, George Gitchel, Caitlin Jones, Sunchai Khemalaap, Valerie Larson, Tiffany Lewis, Scott McDonald, Tamara McKenzie-Hartman, Frank Mierzwa, Alison Molitor, Joe Montanari, Johnnie Mortenson, Nicholas Pastorek, Judy Pulliam, Risa Richardson, Callie Riggs, Rachel Rosenfield, Sara Salkind, James K. Sickinger, Taylor Swankie, Nancy Temkin, Doug Theriaque, Maya Troyanskaya, Rodney Vanderploeg, and Carmen Vasquez.

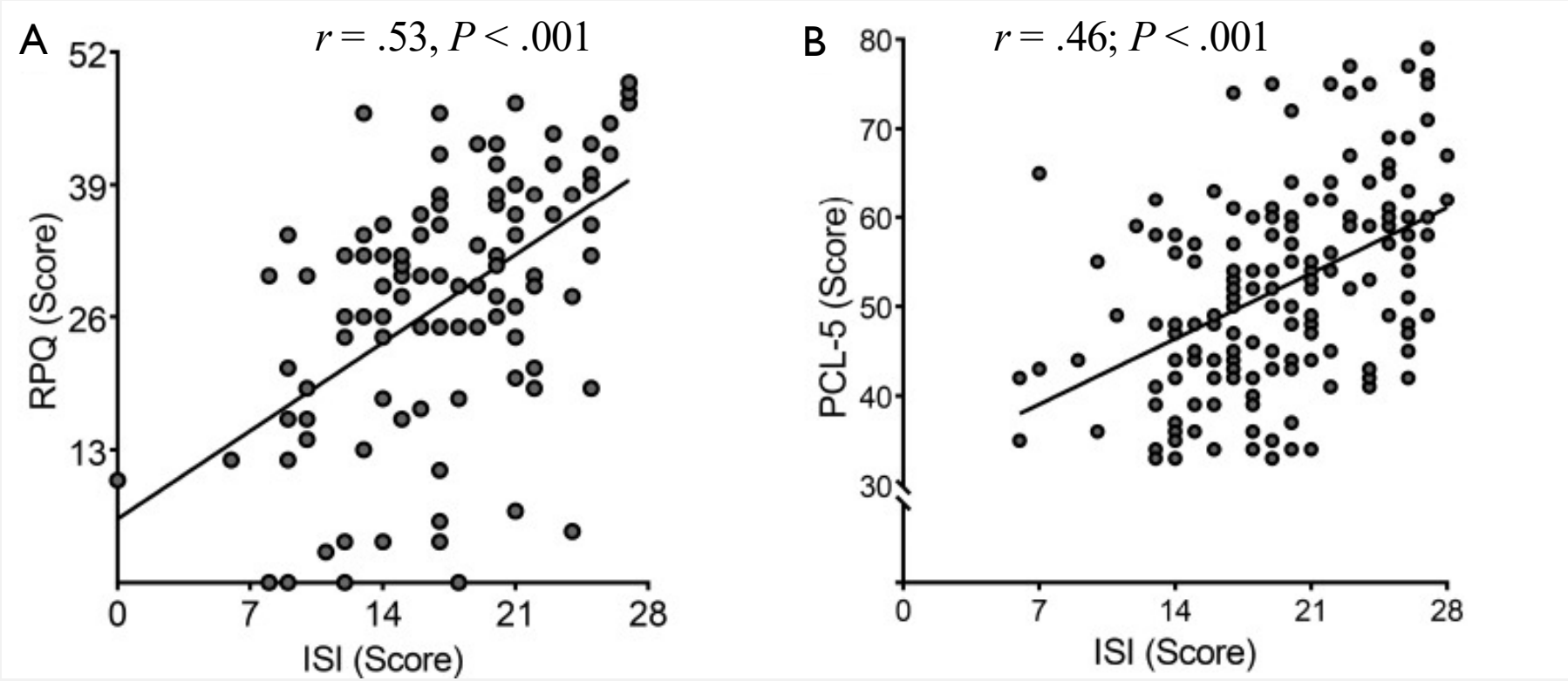
Sorana Raiciulescu, MSc (USU bioinformatics)

Thank you! kent.werner@usuhs.edu & kimbra.kenney@usuhs.edu

EXTRAS

PTSD SYMPTOMS ARE STRONGLY CORRELATED WITH SLEEP DYSFUNCTION AFTER TBI

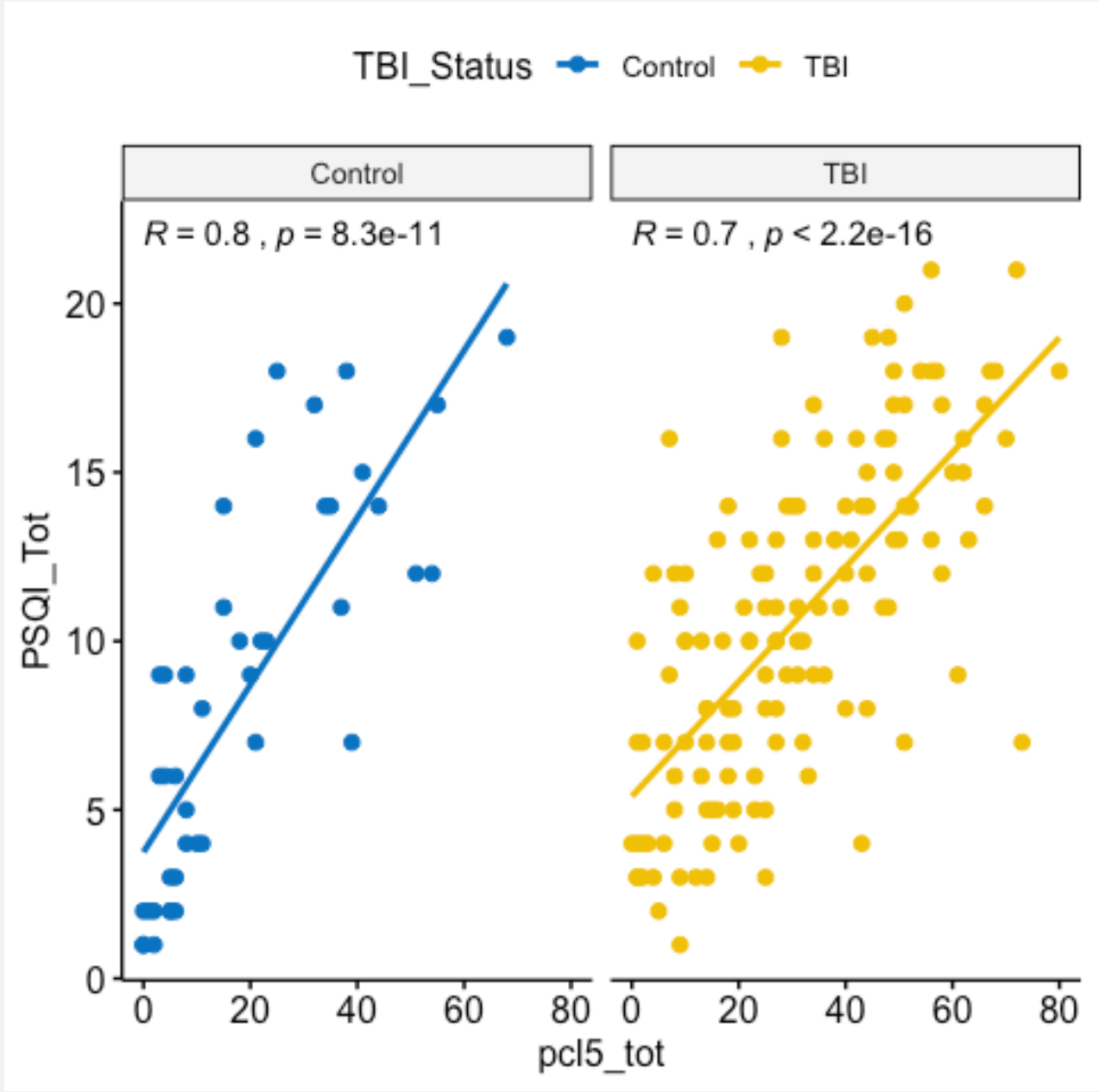
N (total) =	639
No TBI/No PTSD:	383
TBI only:	67
PTSD only:	126
TBI+PTSD:	63



Balba NM et al. J Clin Sleep Med. 2018 Nov 15; 14(11): 1865–1878.

Results

PTSD SYMPTOMS CORRELATE WITH SLEEP QUALITY IN TBI AND CONTROLS



Replicating Balba et al. previously shown