Dietary supplementation with branched chain amino acids in Veterans with TBI

Jonathan Elliott, PhD

Sleep Health & Applied Research Program

December 13, 2019

Oregon Health & Science University

VA Portland Health Care System

TBI and sleep disturbances

Insomnia, hypersomnia, circadian rhythm disorders, etc.

Sandsmark, Elliott, & Lim. *SLEEP*, 2017

Prevalence of ~50-70%

Grima *et al*, *J Clin Sleep Med*, 2016
Mathias *et al*, *Sleep Medicine*, 2012

Lack mechanistic-based therapies

Sedative-hypnotics or stimulants

Cognitive behavioral therapy

Acupuncture

Bright light therapy

Sleep hygiene education

Mild TBI

Cortical impairment

Decreased glutamate input to hypothalamus

Orexin/Hypocretin Dysfunction & Sleep-Wake Disturbances

Negative neurologic outcomes (e.g., cognitive dysfunction)

Branched chain amino acids
(Leucine, Isoleucine, Valine)

- **Substrate for 50% of *de novo* glutamate synthesis in the brain**

Sakai *et al, J Neurochem*, 2004
Yudkoff, *Glia*, 1997

Decreased plasma BCAA levels in TBI

Elliott *et al, SLEEP*, 2018
Jeter *et al, J Neurotrauma*, 2013
Aquilani *et al, Arch Phys Med Rehab*, 2003

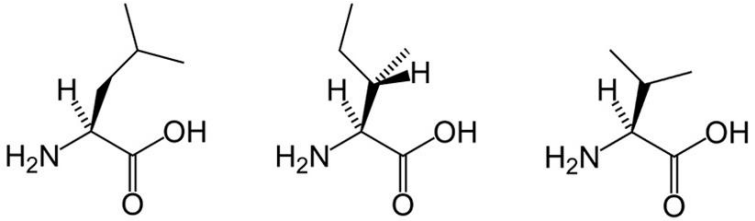
Willie and Lim *et al, J Neurotrauma*, 2012

Restored with BCAA administration and improves outcomes

Aquilani *et al, Arch Phys Med Rehab*, 2005
Aquilani *et al, Arch Phys Med Rehab*, 2008
Ozgulkin *et al, e-SPEN*, 2008
Limet al, *Sci Transl Med*, 2013

Cole *et al, PNAS*, 2010
Elkind and Lim *et al, Frontier Neurology*, 2015
Paterno *et al, J Neurotrauma*

BCAA: metabolism

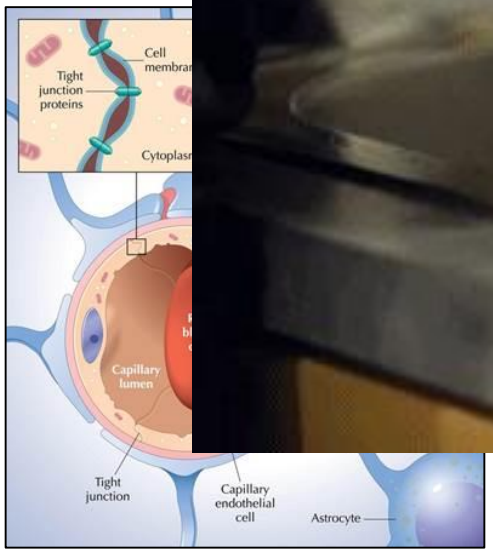


L-Leucine L-Isoleucine L-Valine

Plasma

Matthews,

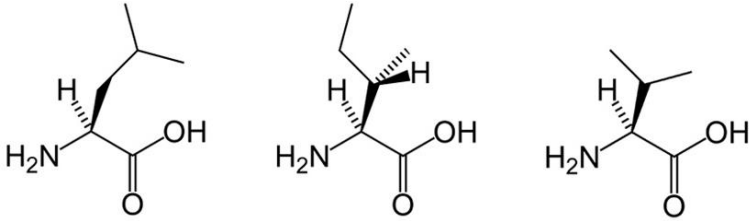
yrosine)



Substrate for ~50% of de novo CNS glutamate synthesis

Sakai *et al, J Neurochem*, 2004
Yudkoff, *Glia*, 1997

BCAA: Pleiotropic benefits



L-Leucine L-Isoleucine L-Valine

1. Improved cognitive function in hepatic cirrhosis and extended exercise

   Horst *et al, Hepatology*, 1984
   Blomstrand, *Amino Acids*, 2001

2. Reduction in manic episodes in bipolar disorder

   Scarna *et al, Br J Psychiatry*, 2003

3. Improvement tardive dyskinesia severity

   Sleep?

   Richardson *et al, Psychopharmacology*, 1999

4. Reduced cachexia in cancer

   Cangiano *et al, J Nat Cancer Inst*, 1996
   Cerra *et al, Crit Care Med,* 1983

5. Restored cortical excitation in ALS and SCA

   Tandan *et al, Neurology*, 1996
   Mori *et al, J Neurol Sci,* 2002

Randomized, double-blind, placebo-controlled trial of dietary BCAA supplementation in Veterans with TBI

Sleep Health & Applied Research Program
research coordinators, technicians, and graduate students





VA Research Pharmacy

Experimental design and timeline

Pre	2 weeks	3 weeks	Post
Initial visit	Baseline	BCAA or placebo intervention	Post-study visit

Informed consent
TBI Interview
Surveys
Neuropsych testing
Blood draw
Actigraphy
Study diary

**Start BCAA or placebo*

Surveys
Neuropsych testing
Blood draw
End actigraphy
End study diary

- **<u>BCAA</u>**
  30 g + flavoring (B.I.D.)
- **<u>Placebo (Rice Protein)</u>**
  30 g + flavoring (B.I.D.)
- Consumed after waking and ~6 hrs later, on an empty stomach
- Block randomized controlling for age by VA Research Pharmacy

BCAA Dosing/Duration

- **5-90 grams, acute**
  well tolerated without any adverse events

Blomstrand *et al, Eur J Appl Physiol*, 1991
De Palo *et al, Amino Acids*, 2001
Gijsman *et al, Psychopharmacology*, 2002
Hasseman *et al, Nutrition*, 1994
Kirvela *et al, Pharmacol Biochem Behav*, 1998
Montgomery *et al, Am J Psychiatry*, 2003
Struder *et al, Horm Metab Res*, 1998
Van Hall *et al, J Physiol*, 1995

- **15-60 grams/day for 7 days to 12 months**
  mild gastrointestinal discomfort noted in one study

For Review:
Fernstrom, *J Nutri*, 2005
Fernstrom, *Amino Acids*, 2013

- **5 days to see improvements in mice**
  100 mMol = 0.36 g/kg/day = ~25 g/day for a 70 kg human

Elkind and Lim *et al, Frontiers in Neurology*, 2015

Demographics

Summary: Demographics		
	BCAA	**Rice Protein**
n	7	7
Age, yr	48 ± 9	49 ± 11
Sex, n=female	2	4
BMI, kg/m2	35 ± 5	36 ± 4
PCL, n≥33	2	2
OSA, n=yes	3	3
Exercise, n>30 min	6	4
Retired/disability	5	4

Feasibility and acceptability metrics

- <u>Dropout rate:</u>
  - 13% withdrawal rate (mainly from a lack of time)

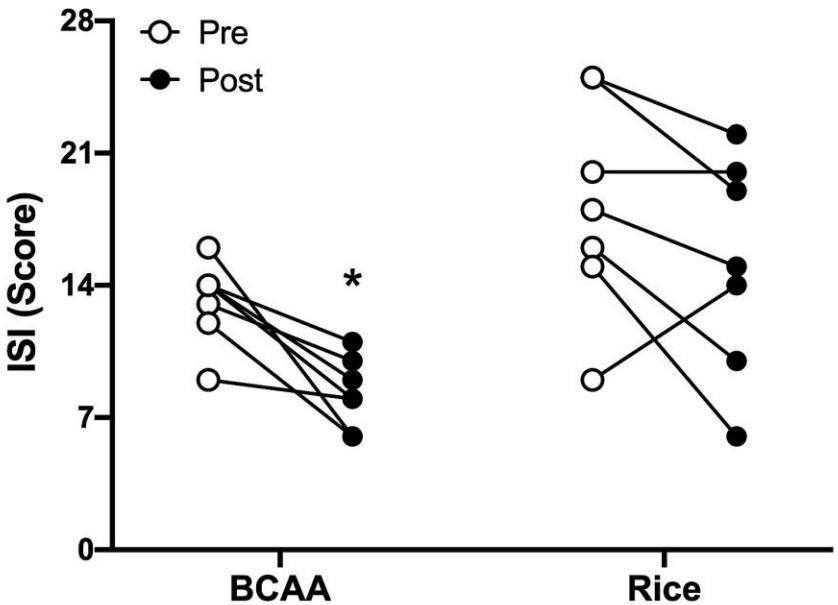
- <u>Adherence:</u>
  - 100% self-reported adherence to supplement
  - 98% days with actigraphy worn

- <u>Summary of BCAA side effects:</u>
  - 2 of 7 reported transient nausea
  - 3 of 7 reported weight loss/appetite suppression
  - 1 of 7 noted increased muscle bulk in leg post-injury

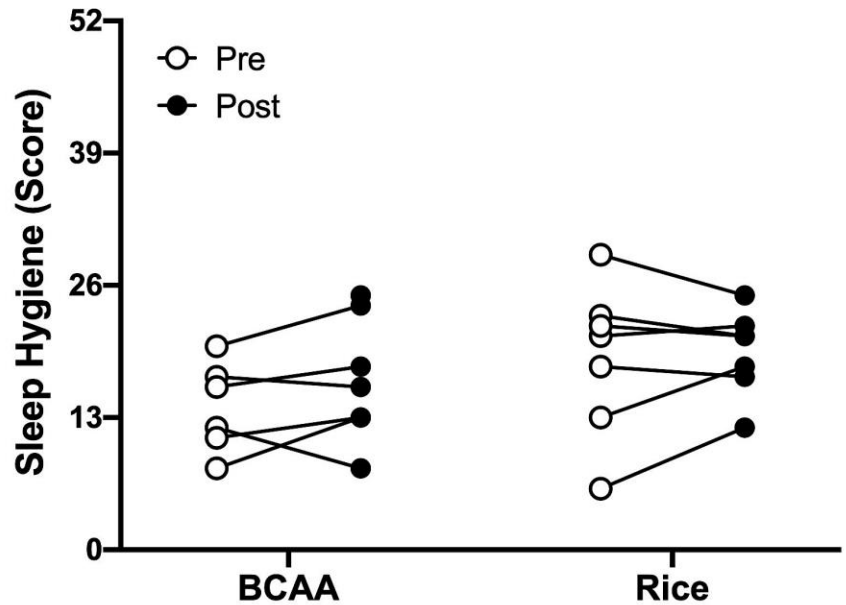
Questionnaires

	Questionnaire	Purpose	Items
Sleep	★ Sleep Hygiene Index (SHI)	Assess sleep habits, scores a participant's sleep hygiene	13
	★ Functional Outcomes of Sleep (FOSQ)	Assess the impact of excessive sleepiness on functional outcomes	11
	★ Insomnia Severity Survey (ISI)	Measures insomnia from none/mild to severe	7
	Morningness-Eveningness Questionaire (MEQ)	Measures chronotype, determines if participant is a "morning" or "evening person"	5
Mood TBI PTSD	Patient Health Questionnaire (PHQ-9)	Assist the clinician in making the diagnosis of depression from mild to severe	10
	PTSD Checklist (PCL-5)	Assess the presence and severity of PTSD symptoms from mild to severe	20
	Neurobehavioral Symptoms Inventory (NSI)	Evaluation of post-concussive symptoms following TBI	22
	NIH PROMIS Emotional-distress-anxiety	Assess self-reported fear, hyperarousal and somatic symptoms related to arousal	4
Quality of life	★ World Health Organization Disability Assessment Scale (WHODAS 2.0)	Measuring health and disability across cultures, gives as a percentage	15
	NIH PROMIS Global Health	Assesses an individual's physical, mental, and social health	10
	NIH PROMIS Pain Interference	Assess self-reported consequences of pain on relevant aspects of one's life	4
	NIH PROMIS Pain Intensity	Assess how much a person hurts	3
	NIH PROMIS Cognitive Function	Assess patient-perceived cognitive deficits	4
	NeuroQoL Participation	Adult ability to Participate in social roles	8
	NeuroQoL Satisfaction	Adult satisfaction with social roles and activities	8

Improved insomnia with BCAA supplementation



P = 0.0045



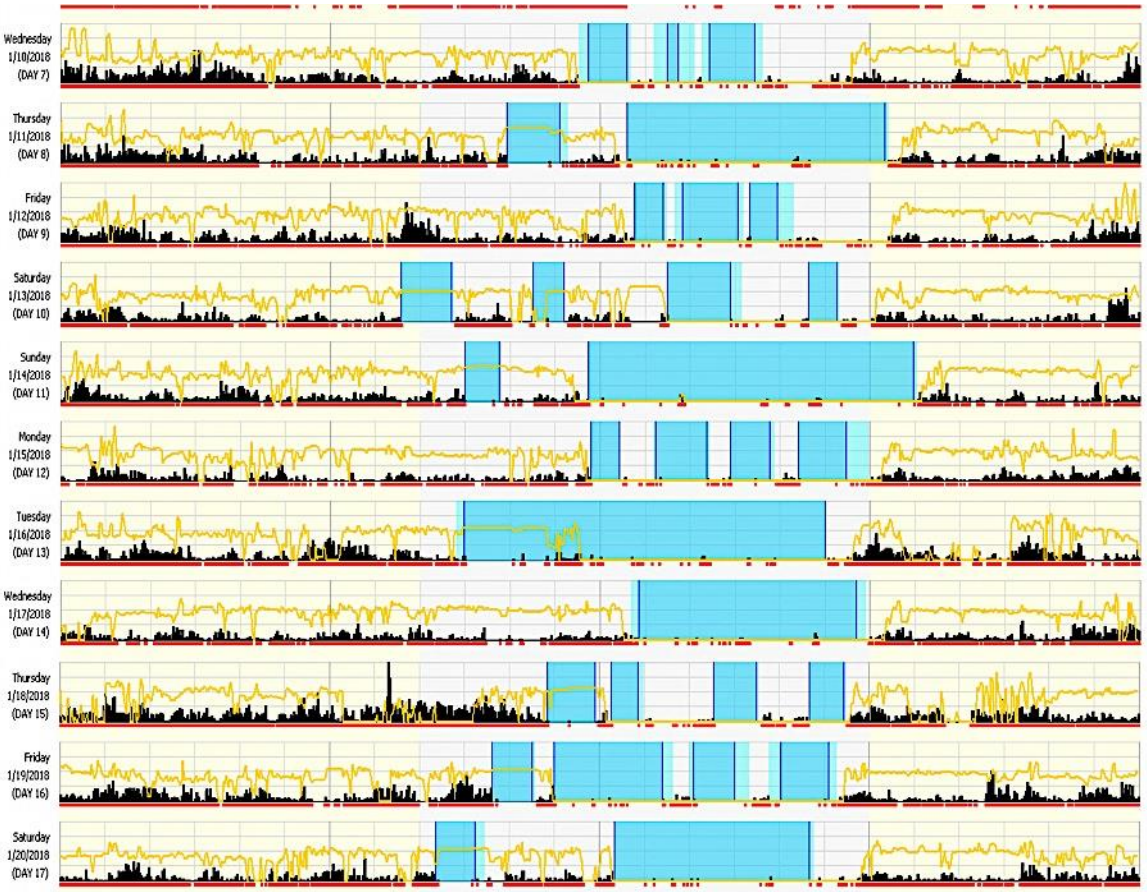
<u>Other trending questionnaire data:</u>

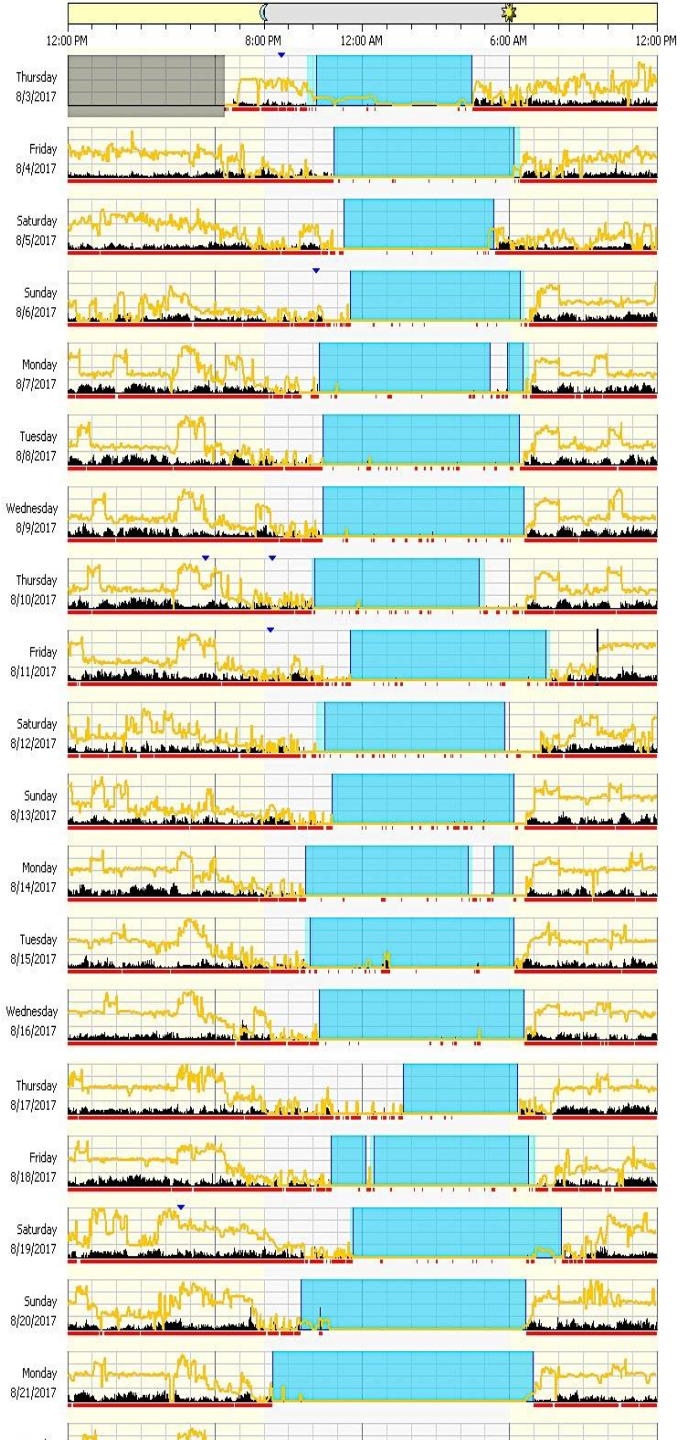
*Functional Outcomes of Sleep Questionnaire: ~15% in BCAA vs ~4% in Rice

*World Health Organization Disability Scale: ~7% in BCAA vs ~0% in Rice

Actigraphy

*Decreased sleep onset latency





Summary of BCAA Pilot Study in Veterans

- Short-term BCAA supplementation is feasible and acceptable in Veteran subjects
- BCAA significantly improve self-reported insomnia
- VA Merit Proposal: Limited efficacy, longer duration, 3 doses (20, 40, 60g), PSG/EEG

Portland VA/OHSU:

Miranda Lim, MD, PhD
Jonathan Elliott, PhD
Carolyn Jones, PhD
Kris Weymann, PhD, RN
Peyton Wickham, BSc
Alisha McBride, BSc
Randall Olson, BA
Nadir Balba, MS
Cadence Michel, BA
Kate Gutowsky, BA

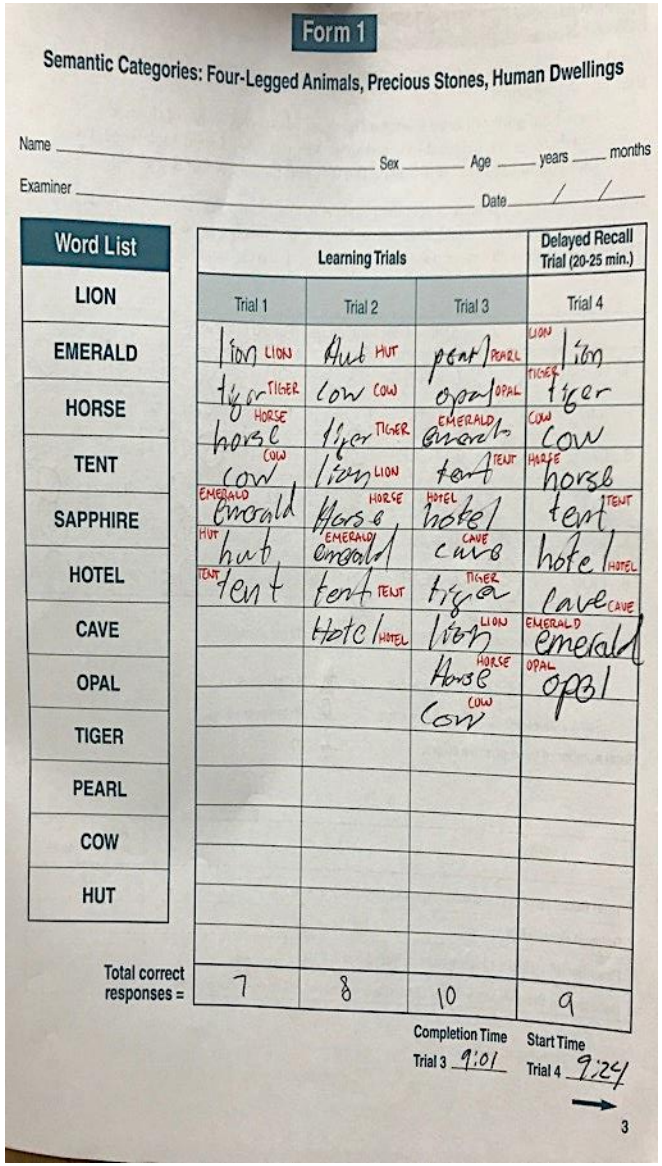
Collaborators:

Mo Modarres, PhD
Risa Richardson, PhD
Megan Callahan, PsyD
Mary Heinricher, PhD
Matt Butler, PhD

Current support:

VA BLRD & RRD Career Development Award
VA RRD SPiRE and Merit Award
Department of Defense PH-TBI Award
USUHS/CNRM/DoD Award
NIH NIA
NIH BUILD EXITO Institutional Core
Oregon Institute of Occupational Health Sciences
National Science Foundation
Portland VA Research Foundation
OHSU Medical Research Foundation

Neuropsych: WAIS-IV, HVLT, DKEFS, COWAT



Form 1

Semantic Categories: Four-Legged Animals, Precious Stones, Human Dwellings

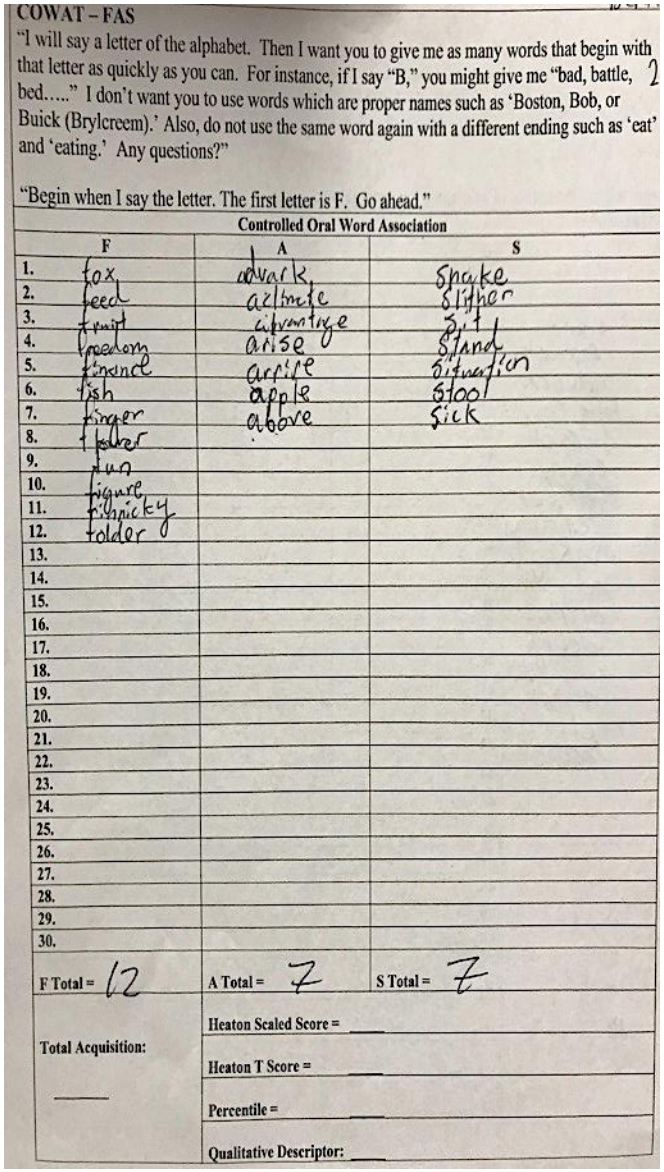
Name _____ Sex _____ Age _____ years _____ months

Examiner _____ Date ___/___/___

Word List	Learning Trials			Delayed Recall Trial (20-25 min.)
	Trial 1	Trial 2	Trial 3	Trial 4
LION	lion LION	Hut HUT	pearl PEARL	LION lion
EMERALD	tiger TIGER	cow COW	opal OPAL	TIGER tiger
HORSE	horse HORSE	tiger TIGER	EMERALD emerald	COW cow
TENT	cow COW	lion LION	tent TENT	HORSE horse
SAPPHIRE	EMERALD emerald	Horse HORSE	HOTEL hotel	TENT tent
HOTEL	HUT hut	EMERALD emerald	CAVE cave	HOTEL hotel
CAVE	TENT tent	tent TENT	TIGER tiger	CAVE cave
OPAL		Hotel HOTEL	LION lion	EMERALD emerald
TIGER			HORSE Horse	OPAL opal
PEARL			COW cow	
COW				
HUT				
Total correct responses =	7	8	10	9

Completion Time Trial 3 9:01 Start Time Trial 4 9:24

3



COWAT – FAS

"I will say a letter of the alphabet. Then I want you to give me as many words that begin with that letter as quickly as you can. For instance, if I say "B," you might give me "bad, battle, bed....." I don't want you to use words which are proper names such as 'Boston, Bob, or Buick (Brylcreem).' Also, do not use the same word again with a different ending such as 'eat' and 'eating.' Any questions?" 2

"Begin when I say the letter. The first letter is F. Go ahead."

Controlled Oral Word Association

	F	A	S
1.	fox	aardvark	snake
2.	feed	ultimate	slither
3.	fruit	advantage	sit
4.	freedom	arise	stand
5.	finance	article	situation
6.	fish	apple	stool
7.	finger	above	sick
8.	folder		
9.	fun		
10.	figure		
11.	fingicky		
12.	folder		
13.			
14.			
15.			
16.			
17.			
18.			
19.			
20.			
21.			
22.			
23.			
24.			
25.			
26.			
27.			
28.			
29.			
30.			
	F Total = 12	A Total = 7	S Total = 7

Total Acquisition: _____

Heaton Scaled Score = _____

Heaton T Score = _____

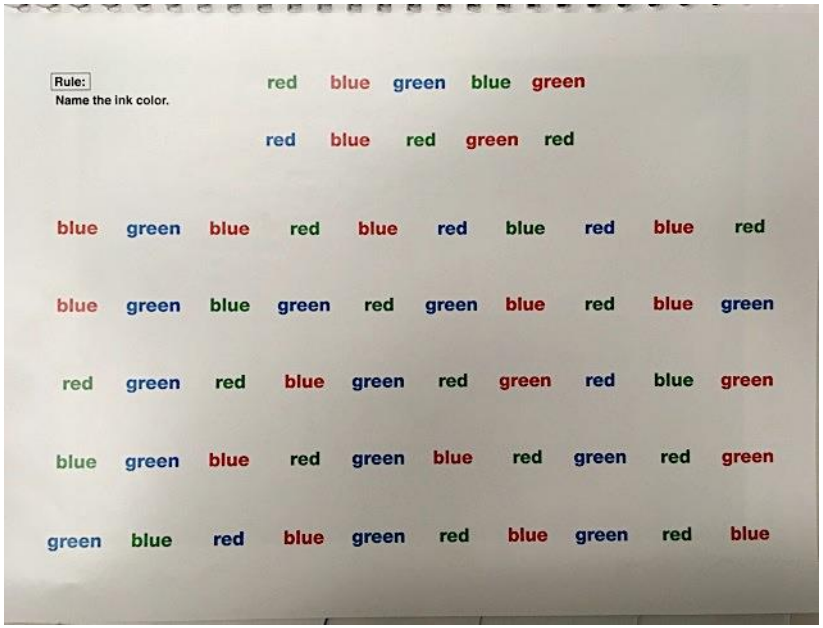
Percentile = _____

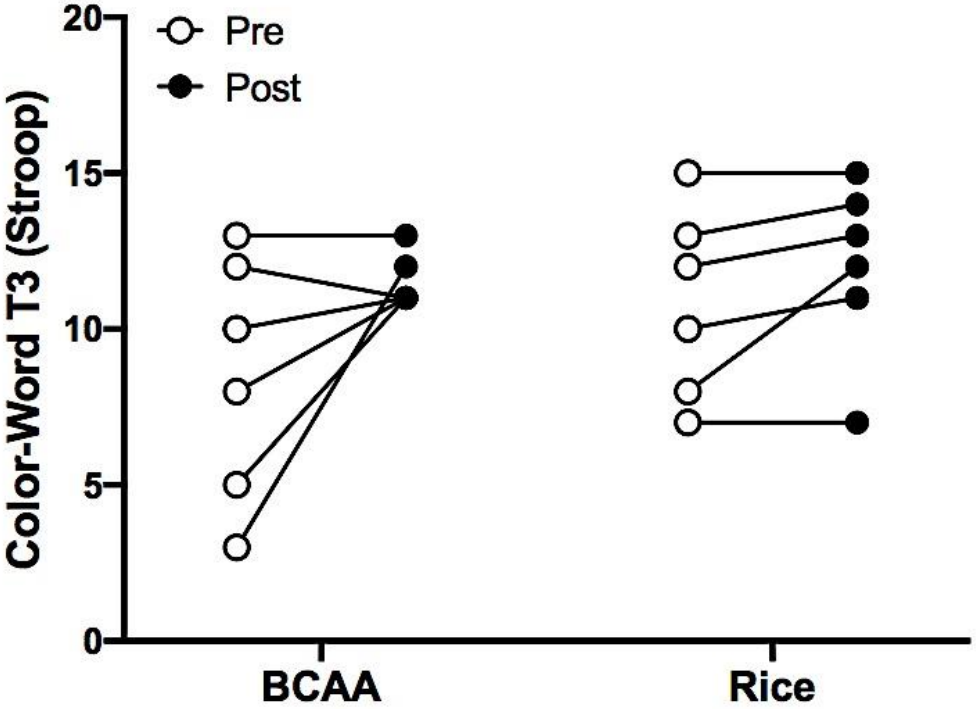
Qualitative Descriptor: _____

Neuropsych trends?

DKEFS Color-Word Interference Test

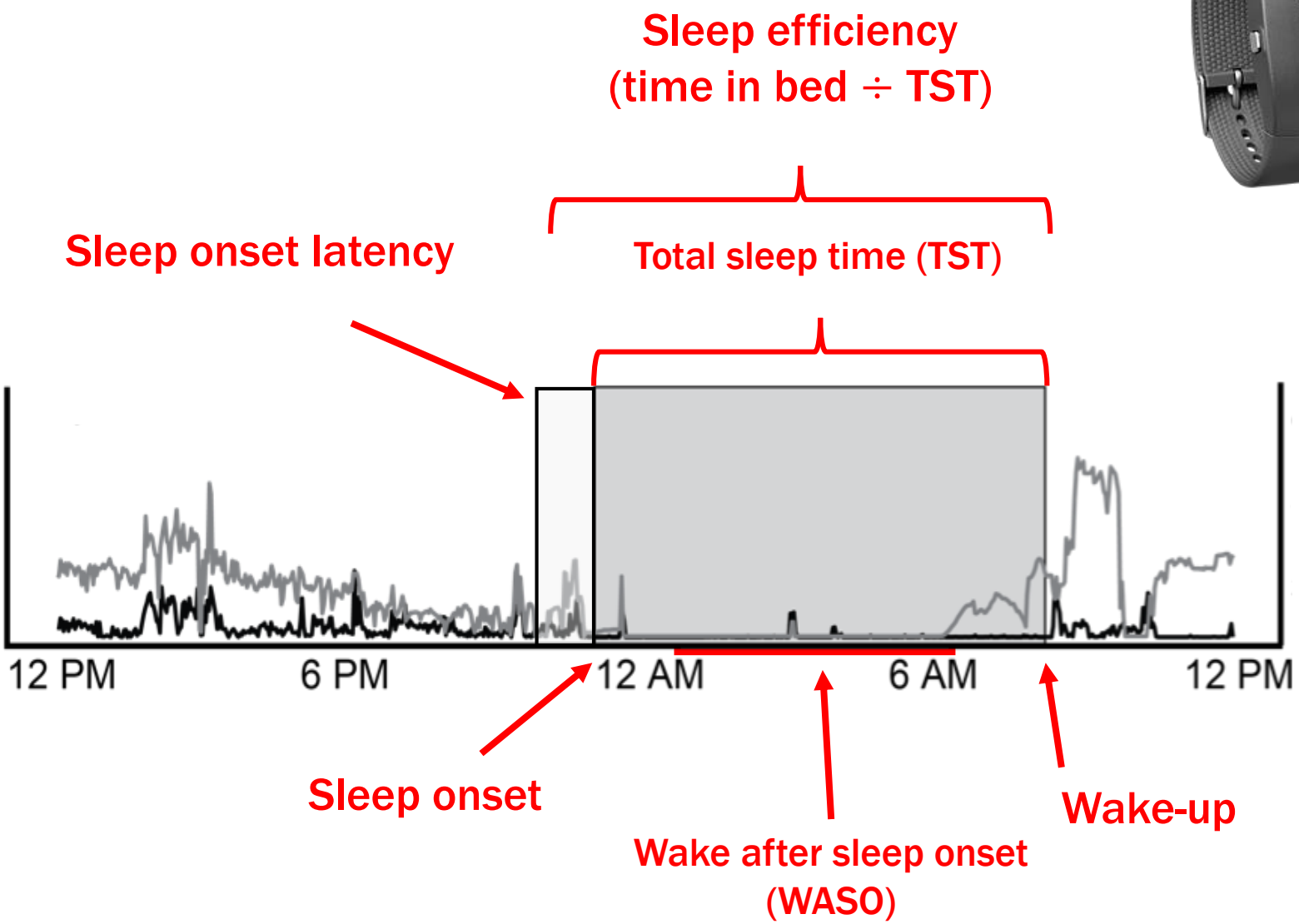
Test 3 (T3): Name the color





P = 0.09

Actigraphy


Sleep efficiency
(time in bed ÷ TST)
Sleep onset latency
Total sleep time (TST)
12 PM
6 PM
12 AM
6 AM
12 PM
Sleep onset
Wake after sleep onset
(WASO)
Wake-up

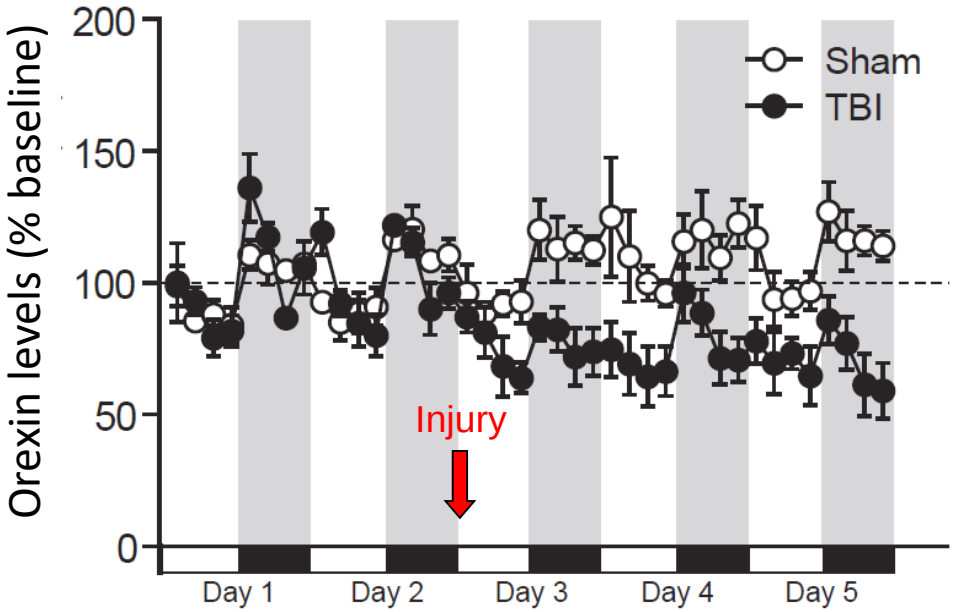
<u>Prior studies:</u>

-BCAA for PKU for 2y

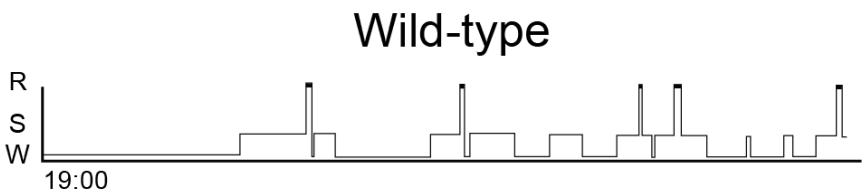
-Safe upper limit of leucine in rats is 8.9 g/kg (~600 g/d in human)

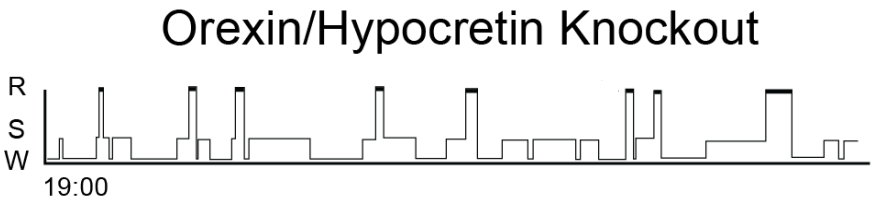
Berry et al., 1982, *Pediatr Res*
Knapik et al., 2016, *Sport Med*
Pencharz et al., 2008, *J Nutr*

Mild TBI causes orexin dysfunction in mice



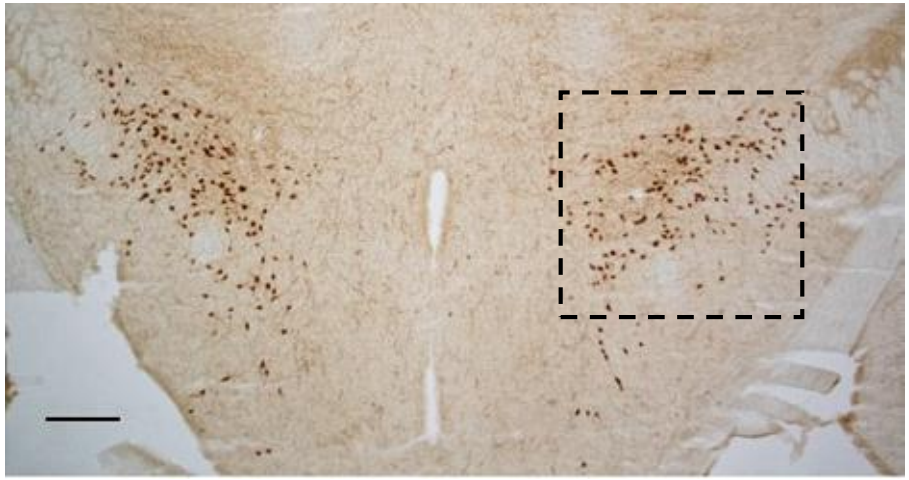
Willie and Lim *et al, J Neurotrauma,* 2012

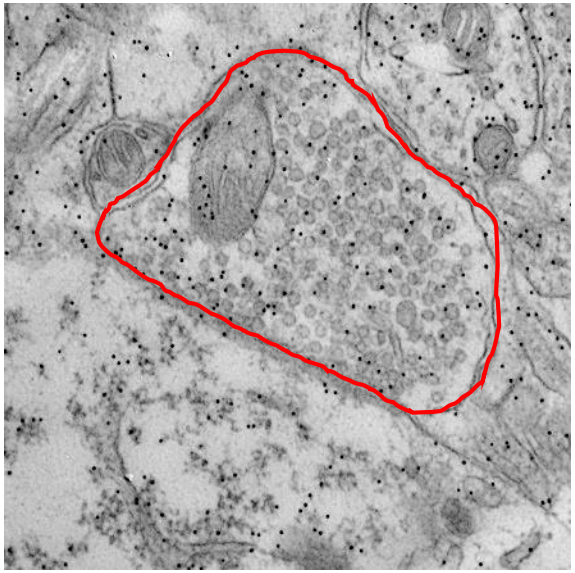


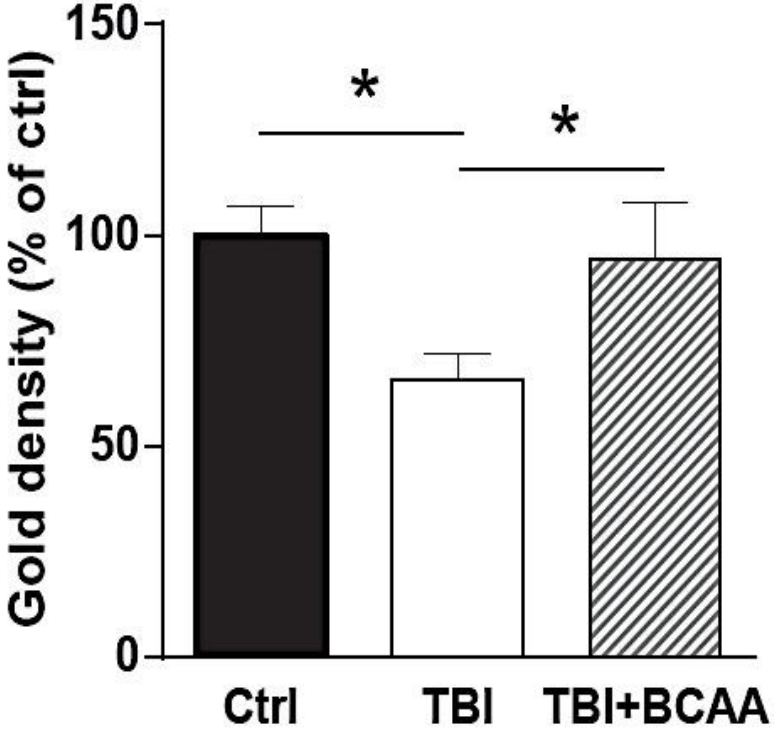


Chemelli *et al, Cell*, 1999

BCAAs increase glutamate within nerve terminals contacting orexin neurons

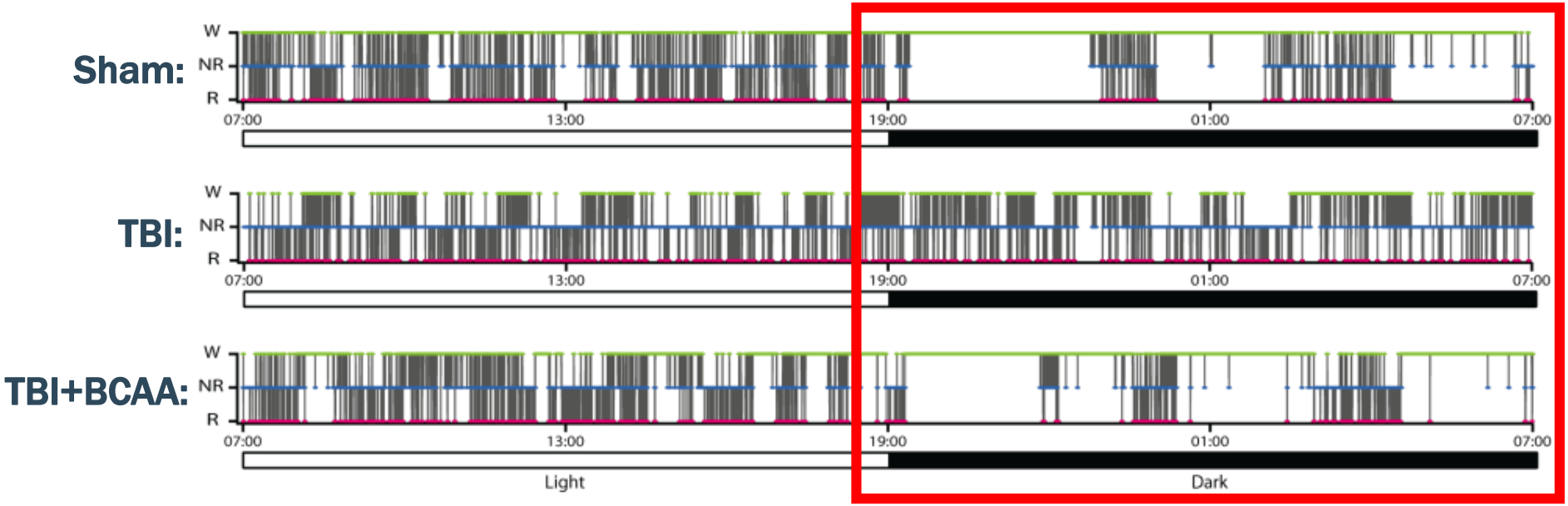


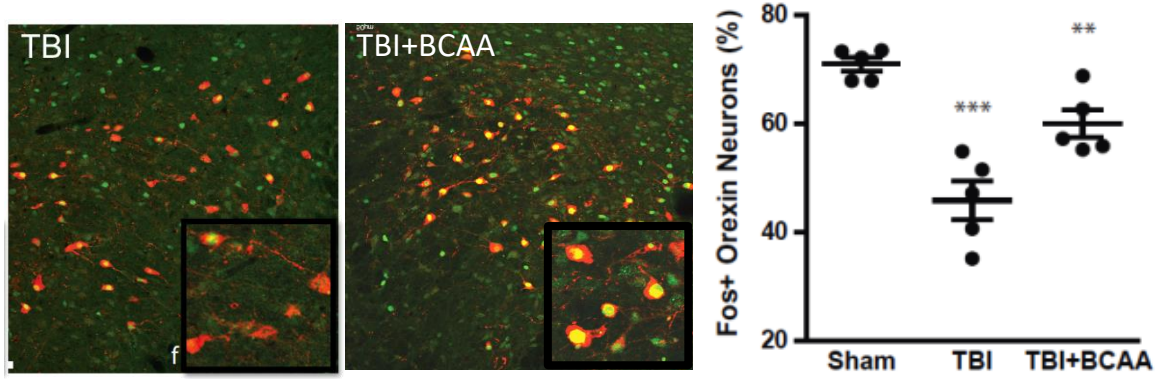




Elliott *et al, SLEEP,* 2018

BCAAs promote wakefulness and restore orexin function after TBI



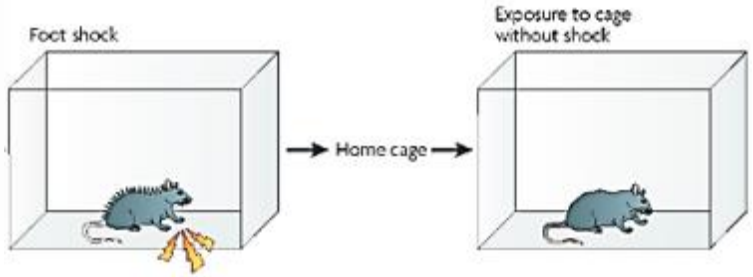


Lim *et al*, *Sci Transl Med*, 2013

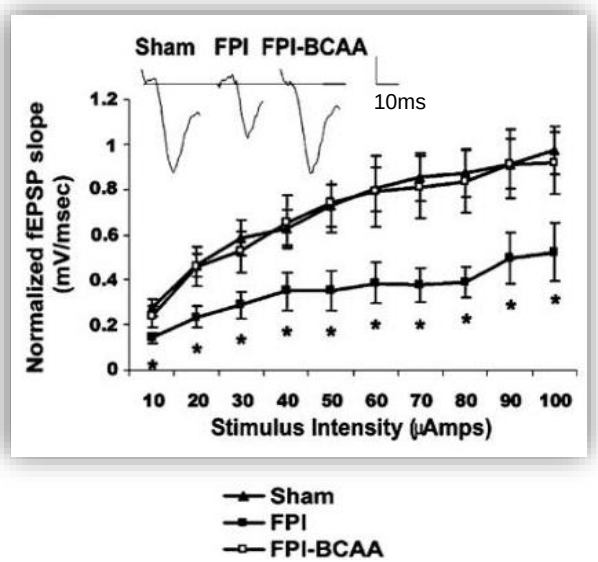
BCAA therapy restores hippocampal physiology and memory

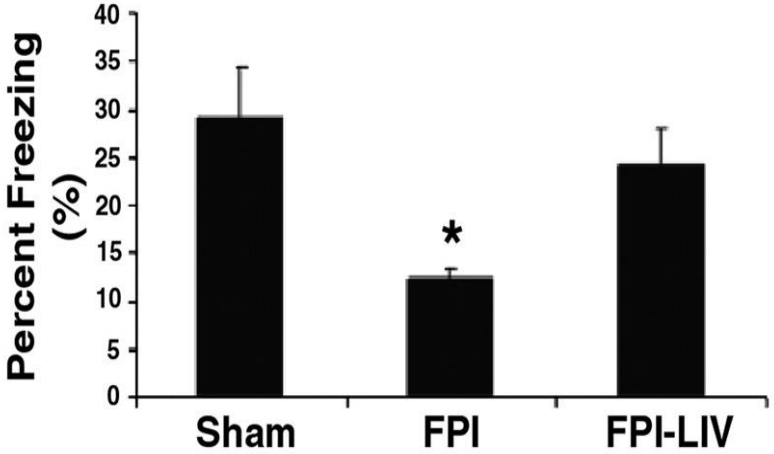
Amino acid	Sham (nmol/mg protein)	FPI (nmol/mg protein)
Valine	16.33 ± 1.64	8.04 ± 1.35*
Leucine	15.03 ± 1.92	7.17 ± 1.48*
Isoleucine	10.19 ± 0.51	8.04 ± 0.96*†
Threonine	2.58 ± 1.30	3.91 ± 0.95
Citrulline	0.18 ± 0.12	0.41 ± 0.91
Tyrosine	1.87 ± 0.26	1.07 ± 0.79
Phenylalanine	0.08 ± 0.01	0.05 ± 0.02

Contextual fear conditioning:



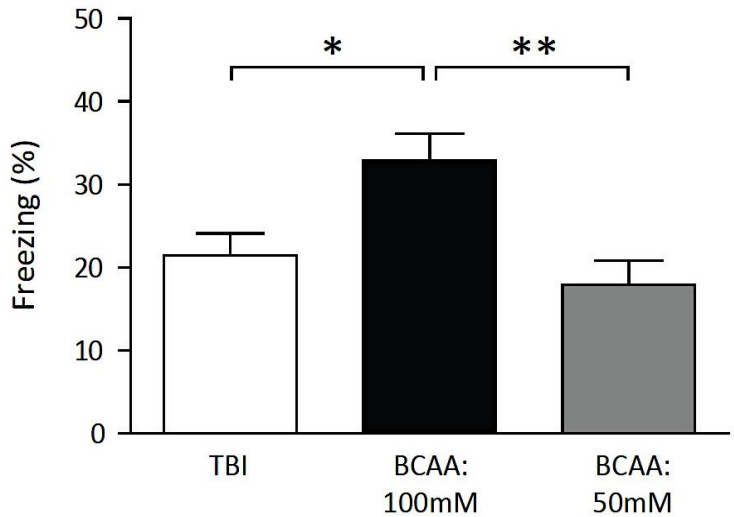
Slice electrophysiology:

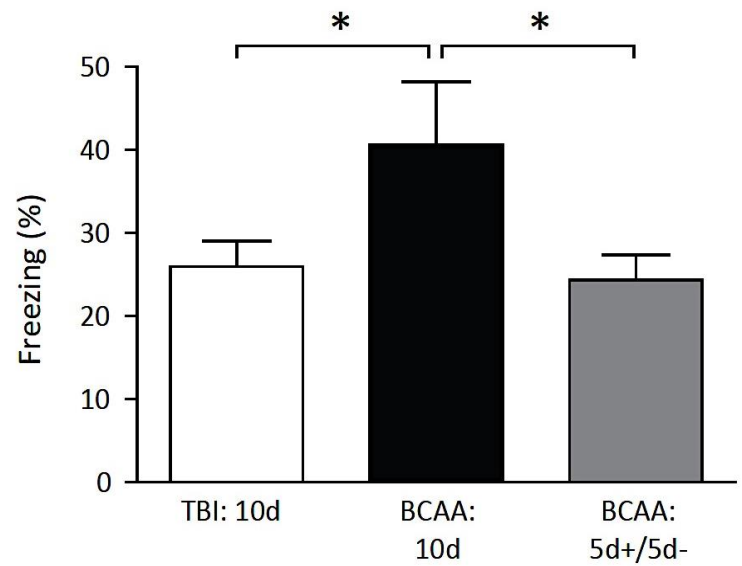


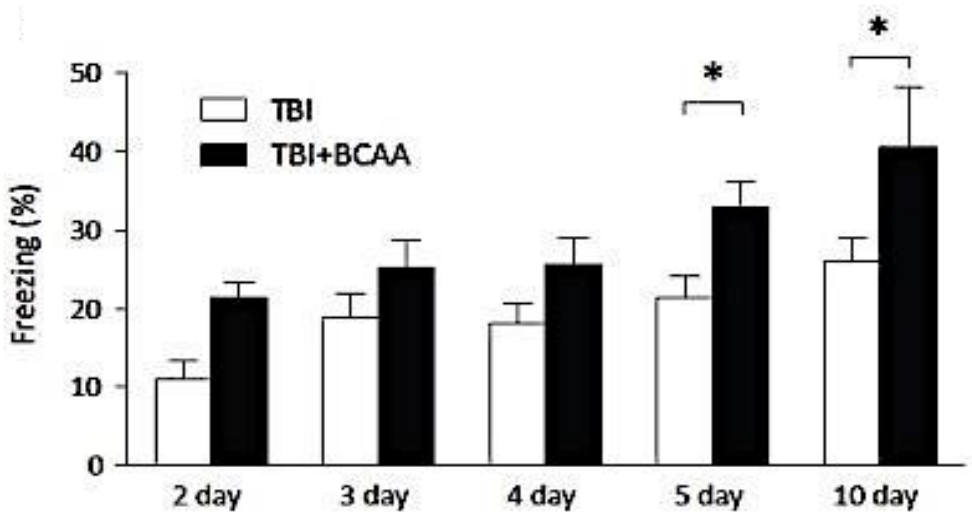


Cole *et al*, *PNAS*, 2010

BCAA Dosing Experiments

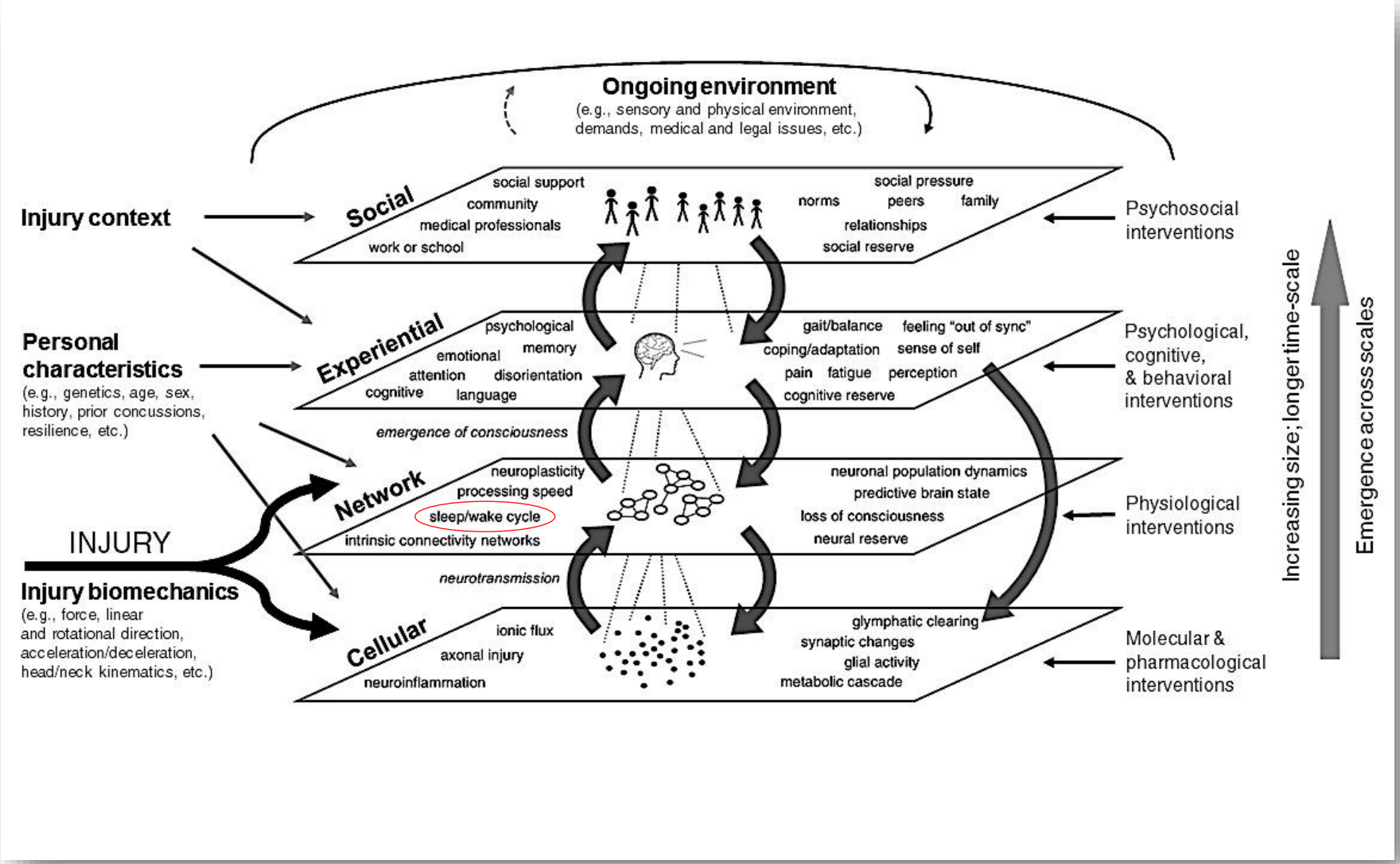






Elkind and Lim *et al*, *Frontiers Neurology*, 2015

mTBI as a multi-scale, complex system



Erin Kenzie, Elle Parks, Erin Bigler, Miranda Lim, Jim Chesnutt, Wayne Wakeland, *Front Neurol,* 2017

Daily Study Diary

EXAMPLE **EXAMPLE**

Key

	Option 1	Option 2	Option 3
Asleep:			
In bed but awake:			
Leave all other boxes empty:			

D=Drink

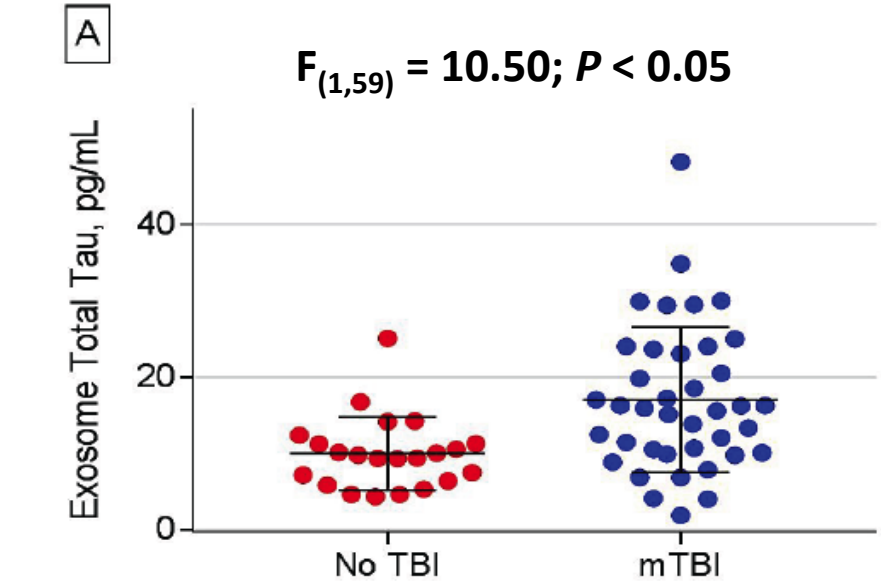
Time of Day

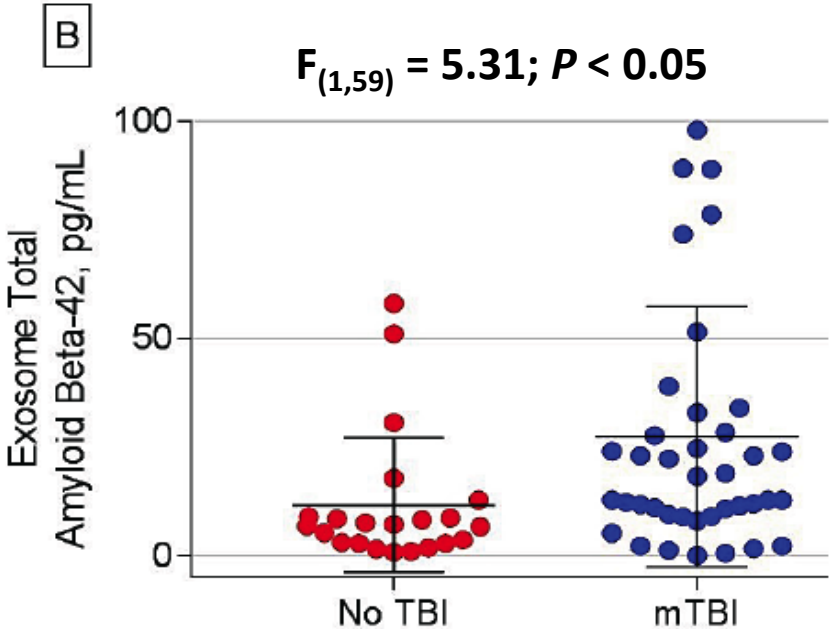
DAY	DATE	TYPE OF DAY Work, school, vacation, off	12	13	14	15	16	17	18	19	20	21	22	23	24	01	02	03	04	05	06	07	08	09	10	11	12	Notes
Tue	7.17.18	Work				D																		D				
Wed	7.18.18	Work				D																	D					
Thu	7.19.18	Vacation				D																		D				
Fri	7.20.18	Vacation					D																		D			
Sat	7.21.18	Vacation					D																	D				
Sun	7.22.18	Off					D																	D				
Mon	7.23.18	Work					D																	D				

Instructions: Indicate the time of day that you are in bed and asleep and the time of day that you are in bed but awake. Each box represents 30 minute increments, there is no need to divide them into smaller increments. Please be consistent in your labeling, see the above key for examples.

Objective adherence: Serum BCAA levels

Blood-based Brain Biomarkers





Courtesy of Jessica Gill

JCSM
Journal of Clinical Sleep Medicine

REVIEW ARTICLES

Sleep Disturbances in Traumatic Brain Injury: A Meta-Analysis

Natalie Grima, DPsych[1,2,4]; Jennie Ponsford, PhD[2,4]; Shantha M. Rajaratnam, PhD[4,5,6]; Darren Mansfield, MD, PhD[3,4]; Matthew P. Pase, PhD[7,8] 2016

Search terms: *TBI* and *Sleep*
Primary outcomes: *Polysomnography metrics*
Secondary outcomes: *Self-report metrics*

- 7,068 articles screened
- 228 potentially relevant

16 studies included

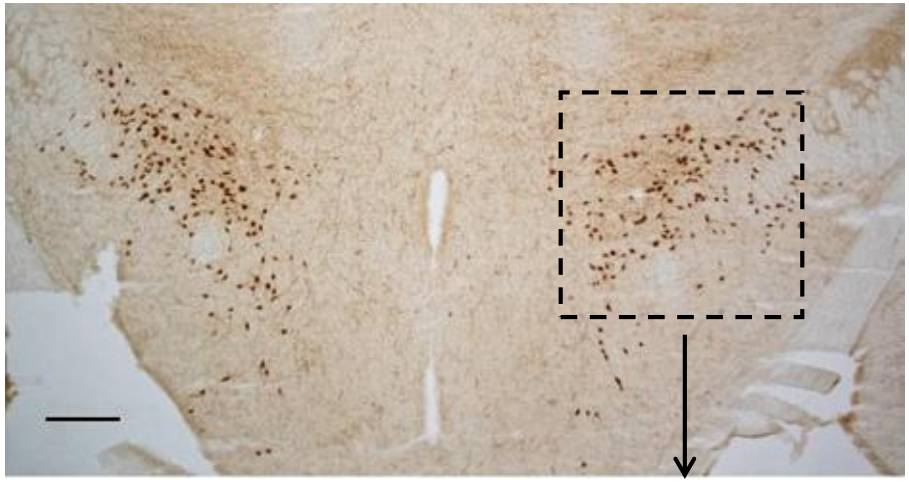
637 TBI patients
32 ± 7 years of age, 71% male

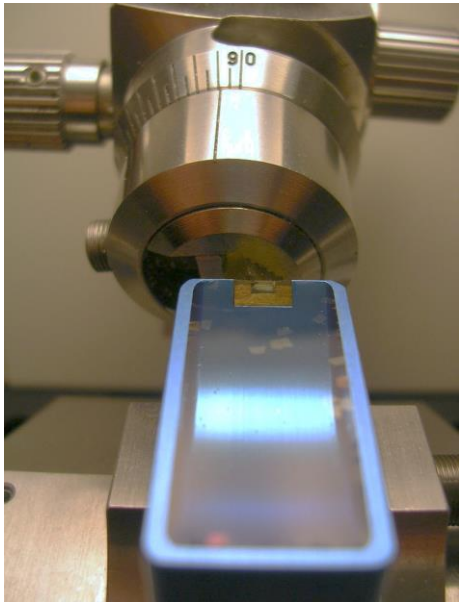
567 controls
32 ± 10 years of age, 66% male

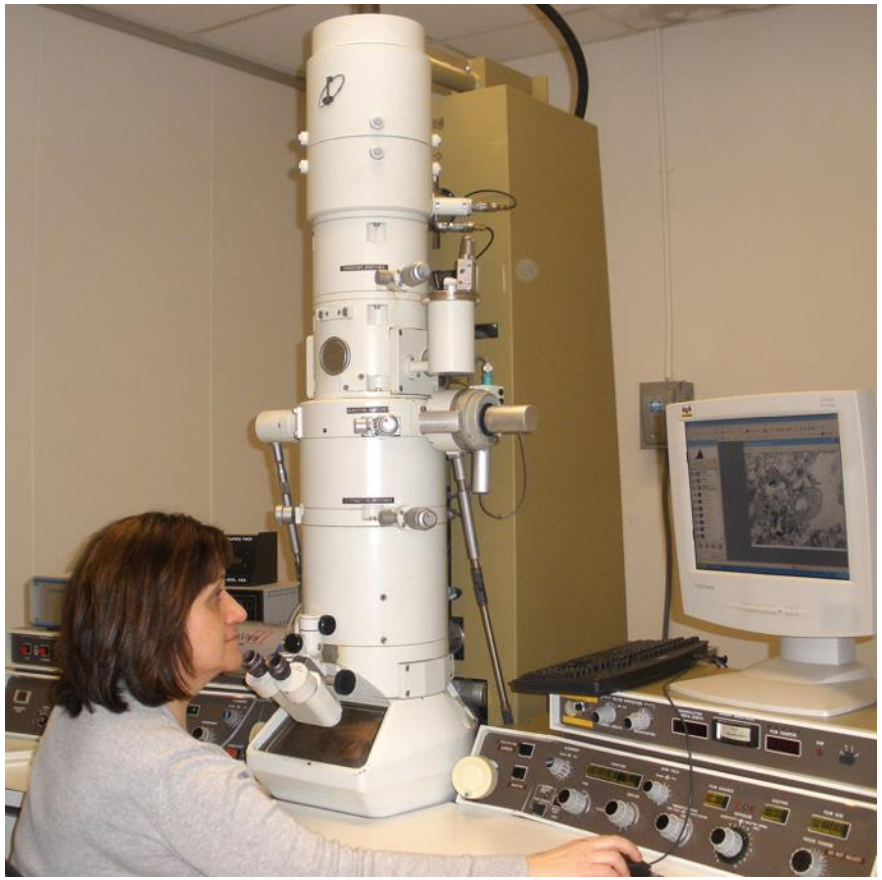
TBI Patients experienced

- Increased wake after sleep onset
- Reduced total sleep time
- Poorer sleep efficiency
- Increased sleep onset latency
- No differences in sleep architecture (trend for reduced REM sleep)
- Higher Epworth Sleepiness Scale scores
- Higher Pittsburg Sleep Quality Index score

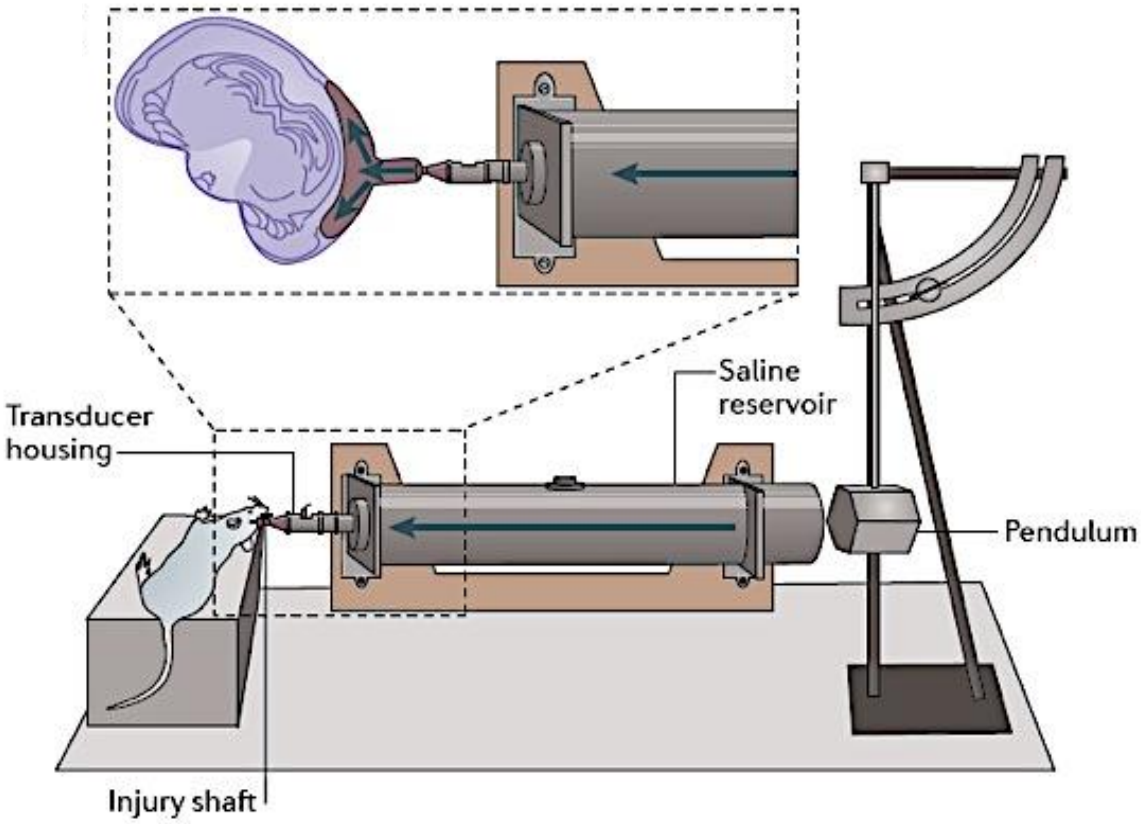
Electron microscopy visualization of glutamate in orexin synapses

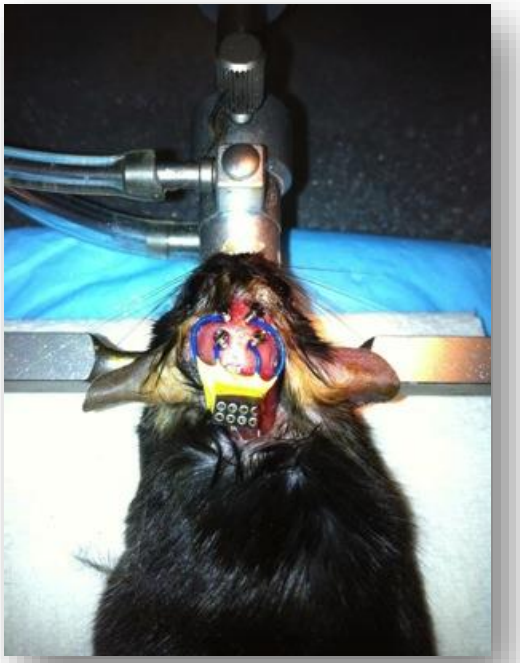




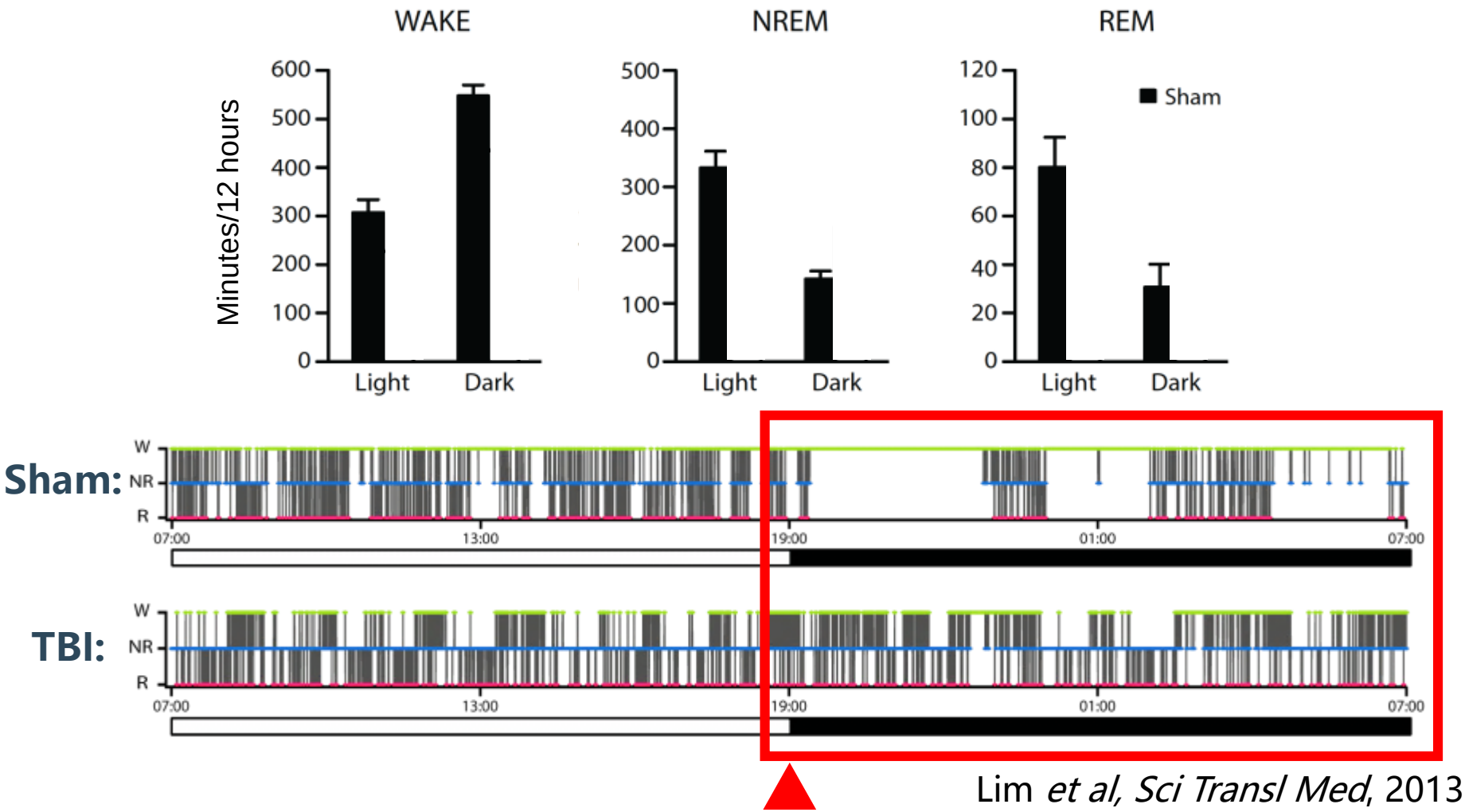


Measuring sleep in a mouse model of TBI



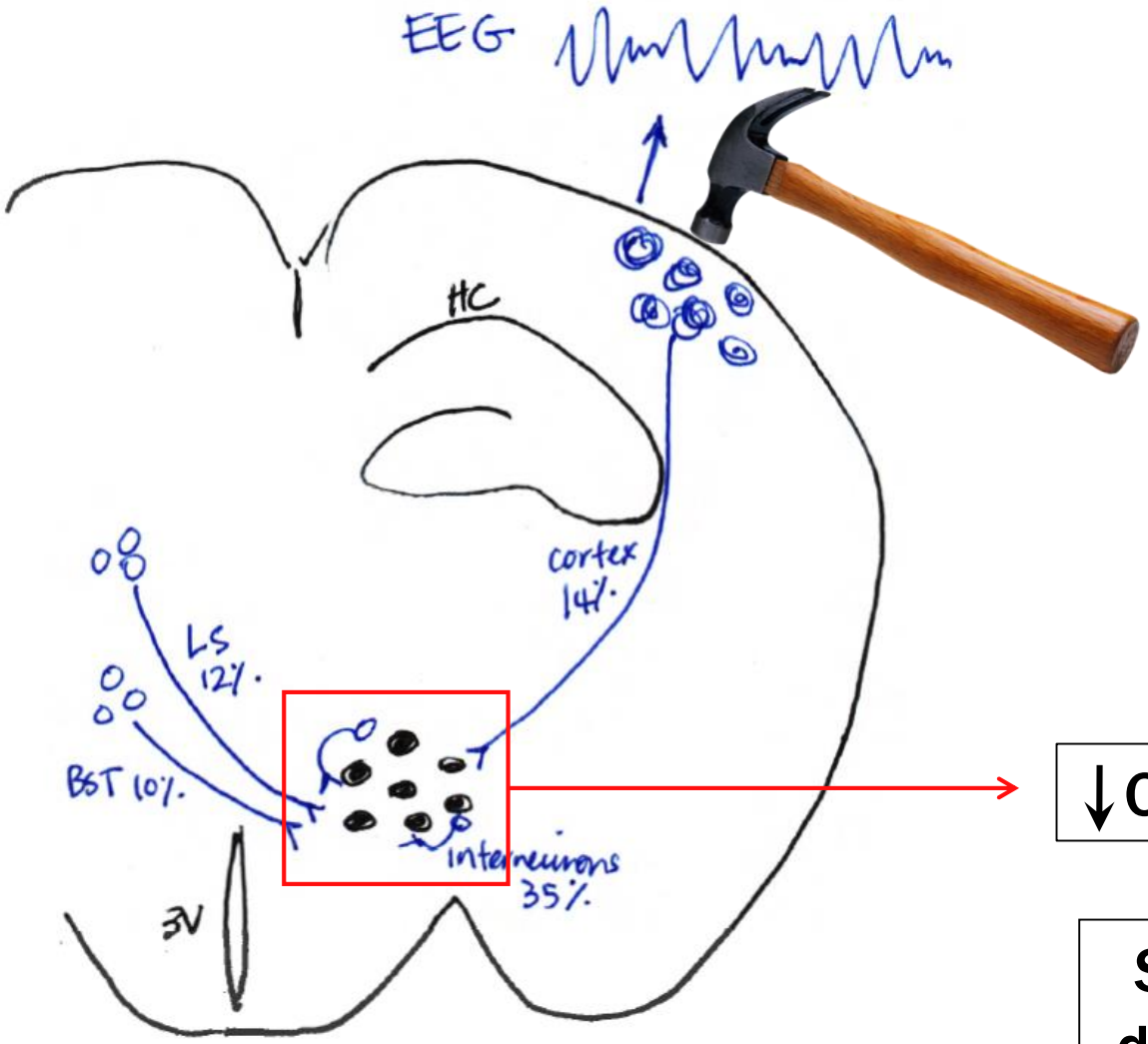


Mild TBI causes sleep-wake impairments in mice



Lim *et al, Sci Transl Med*, 2013

How might mild TBI affect deep orexin neurons?

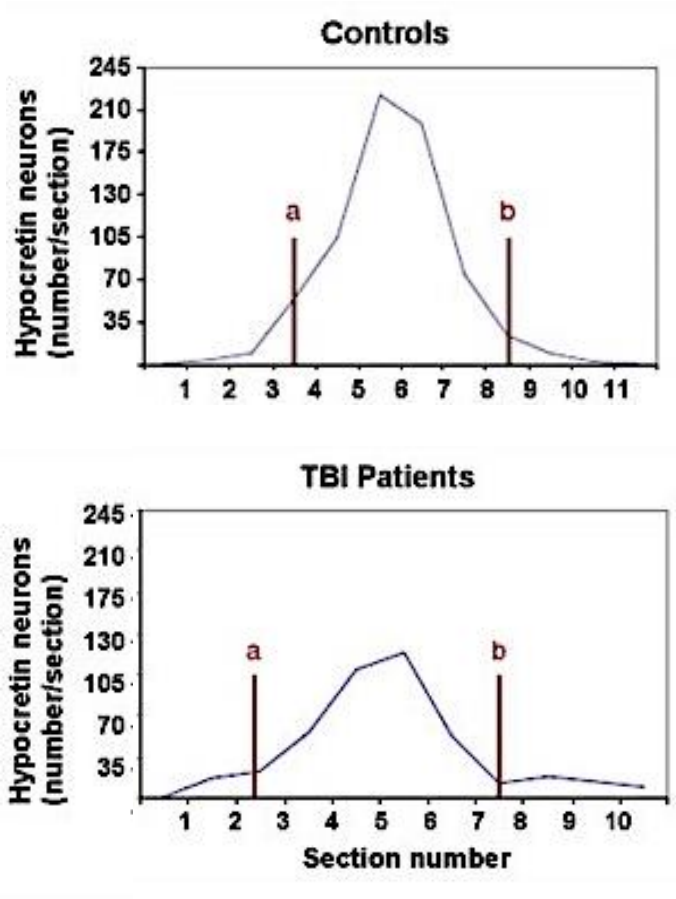


↓Orexin activity

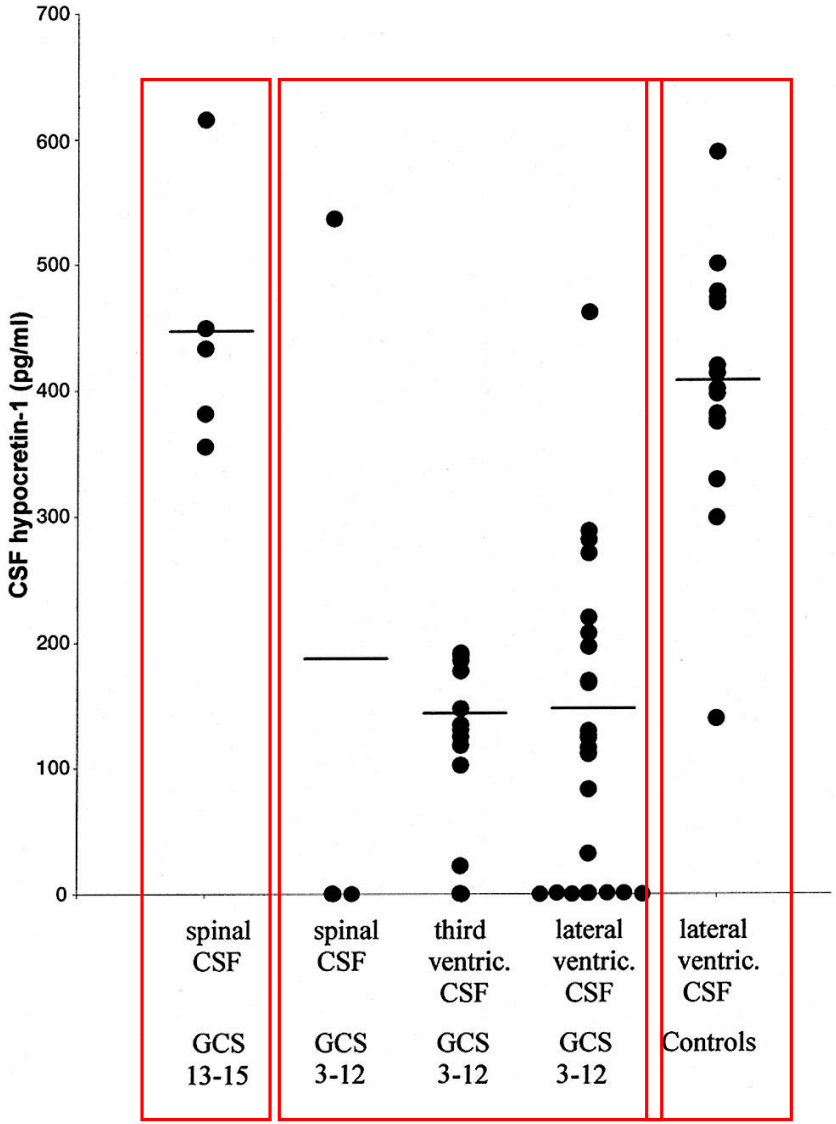
↓

Sleep-wake disturbances

CSF orexin is acutely suppressed after moderate/severe TBI



Baumann *et al, Ann Neurol,* 2009



Baumann *et al, Brain*, 2007

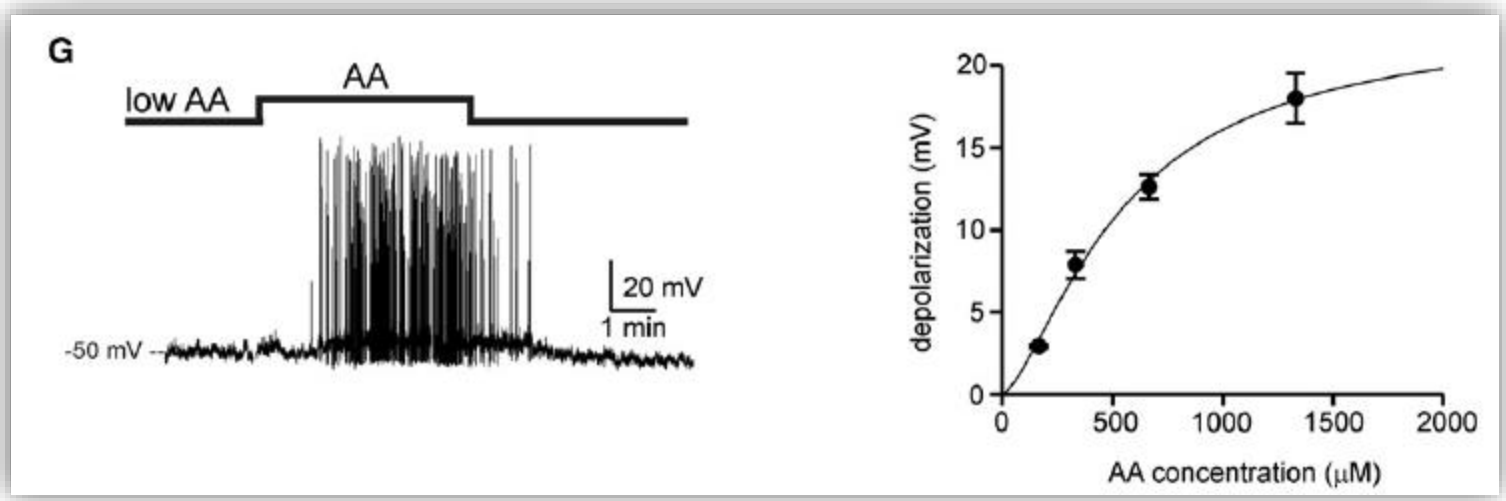
Could BCAA directly activate orexin neurons?

Cell PRESS

Neuron
Article

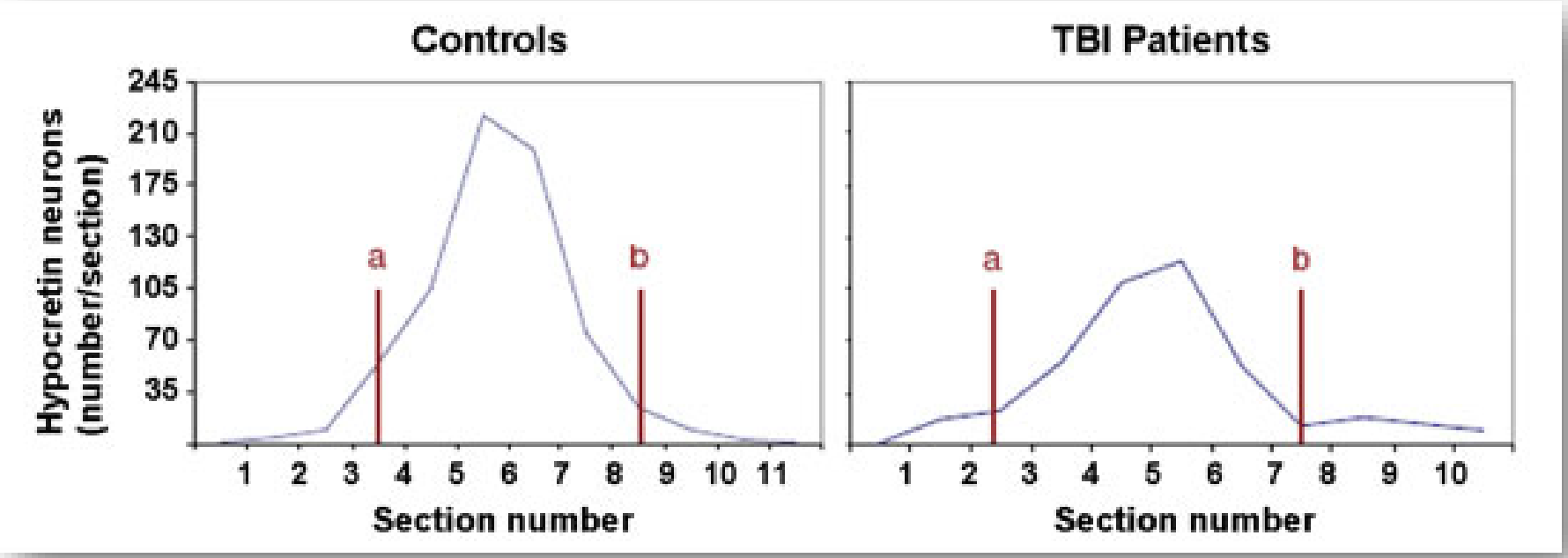
Activation of Central Orexin/Hypocretin Neurons by Dietary Amino Acids

Mahesh M. Karnani,[1] John Apergis-Schoute,[1] Antoine Adamantidis,[2] Lise T. Jensen,[3] Luis de Lecea,[4] Lars Fugger,[5] and Denis Burdakov[1,*]
[1]Department of Pharmacology, University of Cambridge, Cambridge CB2 1PD, UK
[2]Department of Psychiatry, McGill University, Montreal (Quebec) H4H 1R3, Canada
[3]Aarhus University Hospital, Aarhus N 8200, Denmark
[4]School of Medicine, Stanford University, Stanford, CA 94305, USA
[5]Weatherall Institute of Molecular Medicine, University of Oxford, Oxford OX3 9DS, UK
*Correspondence: dib22@cam.ac.uk
DOI 10.1016/j.neuron.2011.08.027



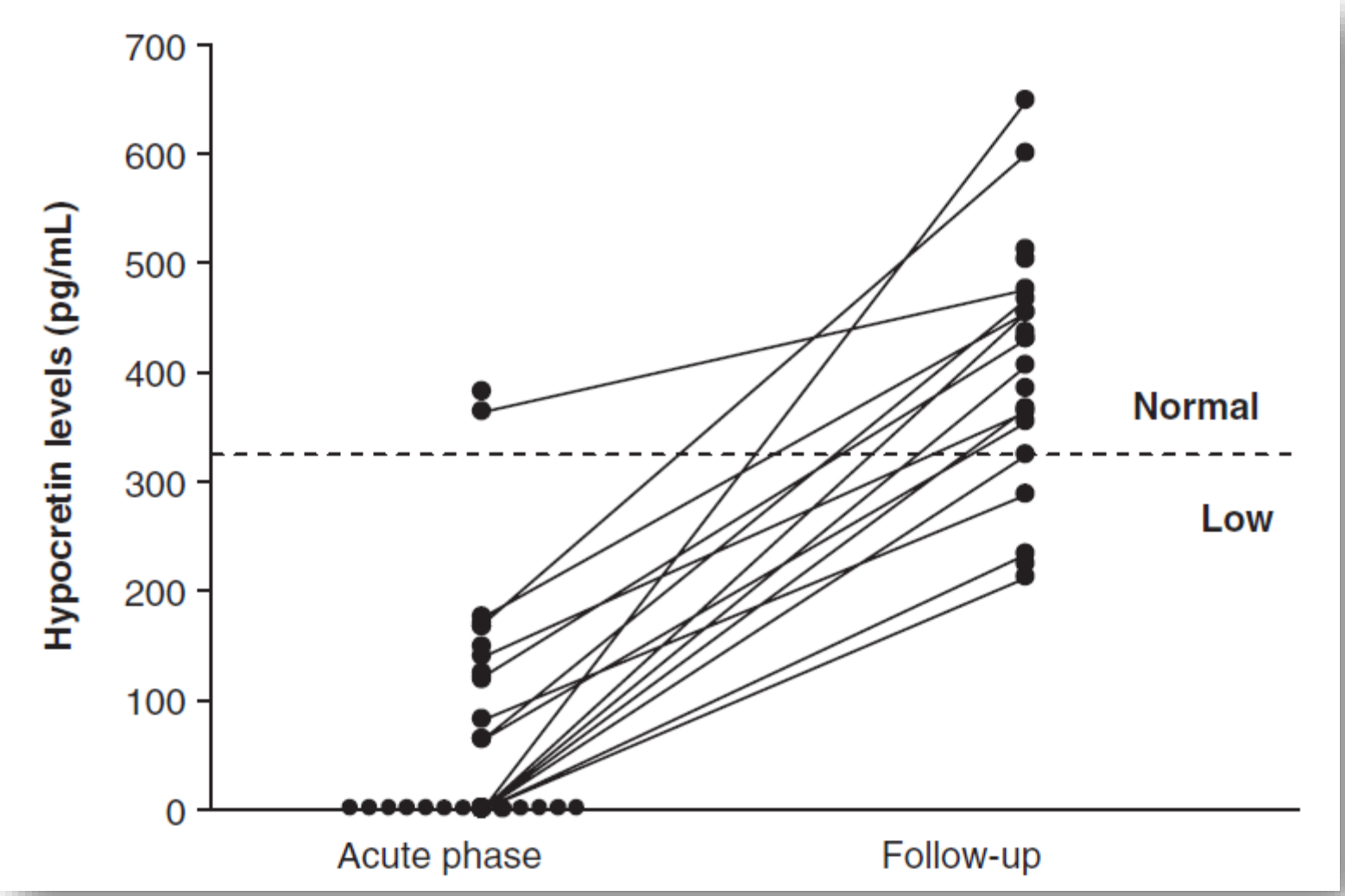
Orexin sensing of macronutrient intake?

Loss of orexin neurons in post-mortem TBI



Baumann et al., 2009, *Ann Neurol*

CSF orexin mostly normalizes after 6 months



Baumann et al., 2007, *Brain*