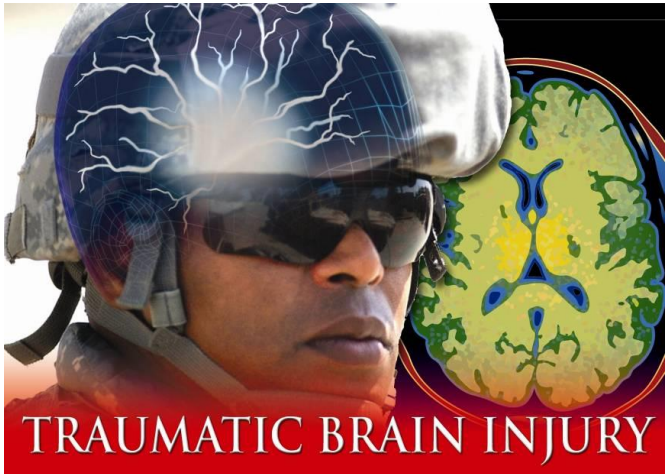
Interface of Sleep and TBI/Concussion

Michael S. Jaffee, MD, FAAN, FANA



DHA Vision

"A joint, integrated, premier system of health, supporting those who serve in the defense of our country."

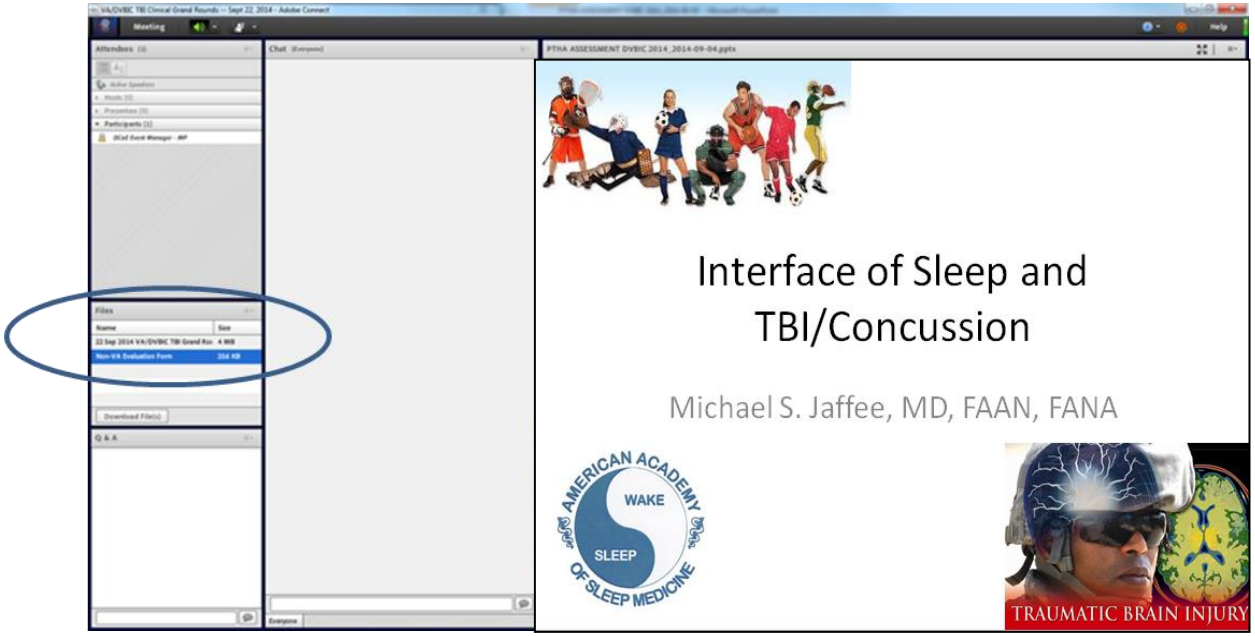
Webinar Details

- Audio is not provided via Adobe Connect
- For Audio
  - Dial In: 888-455-7049
  - Passcode: 7245308
- The webinar is being recorded
- Q&A session is done online at the end of the webinar and participants are to submit them to the Q&A pod only

Resources Available for Download

Defense Health Agency

- Today's presentation will be available for download at the end of the program in the "Files" box on the screen (circled).
- All documents can be downloaded from the Adobe site



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- All attendees are eligible for 1.0 credit hour of ACCME, ACCME-NP, ANCC and APA for 100% attendance.
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VHA Attendee Instructions:

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- For DoD/non-VA participants, you must pre-register for this course on the VHA TRAIN portal at http://vha.train.org
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Webinar Overview

Defense Health Agency

- Sleep disturbance inhibits neural remodeling and prolongs recovery after traumatic brain injury (TBI) by impeding restorative processes that occur during sleep. It can impair cognition, social functioning, rehabilitation and return to work, and it can increase pain and irritability.
- In the first part of a two-part Clinical Grand Rounds series about sleep disturbances, we will discuss the pathophysiology of these disturbances. Using a clinical patient case approach, we will also compare the common challenges for concussion patients to the challenges for those with moderate or severe brain injuries.

Disclosure

- The views expressed in this presentation are those of the presenter and do not reflect the official policy of the Department of Defense or the U.S. Government
  - I do not intend to discuss devices, products or procedures which are off-label, unlabeled, experimental, and/or investigation (not FDA approved)
  - Member of the Data Safety Monitoring Board for Neurohabilitation, Inc. Device Study
  - Author on the White Paper on TBI Rehabilitation for EBM Care (medical informatics company)

Michael S. Jaffee, MD

- Vice chair, Dept. of Neurology and director of the Trauma, Concussion and Sports Neurology program, University of Florida
- Chair of the Sleep Science panel for the American Academy of Neurology
- Board certified in neurology, psychiatry, sleep medicine and brain injury medicine

- Previously, associate professor of neurology, psychiatry, and neurobehavioral sciences at the University of Virginia (UVA)
- Served as the inaugural medical director of the Brain Injury and Sports Concussion Institute and director of the Neurology Sleep Service at UVA
- Retired U.S. Air Force colonel since 2013, served in Iraq as the medical staff chief at a combat support hospital and as a neurology consultant to the U.S. Air Force Surgeon General
- Former director of the Defense and Veterans Brain Injury Center, overseeing 18 sites and championing deployed medical research

Learning Objectives

At the conclusion of this program, learners will be able to:

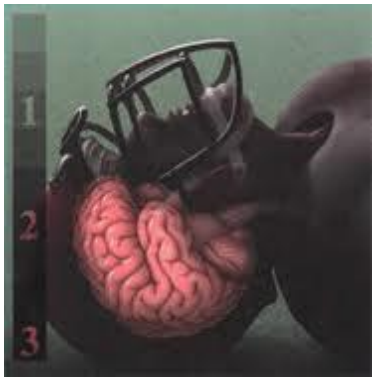
- Differentiate between insomnia and hypersomnia after a TBI
- Describe circadian and sleep quality issues after a TBI
- Recognize sleep disturbance pathophysiology and its impact on TBI recovery

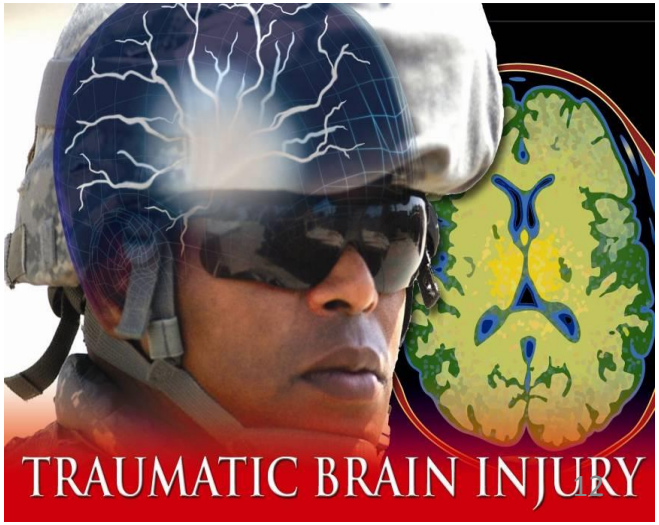
Case Presentation

- 20 yr. old soldier sustains a concussion in a training injury (non-combat)
- Along with headaches and dizziness, he reports hypersomnia for first week following injury
- Headaches and dizziness diminish over the initial week and now he complains of insomnia.
  - He cannot fall asleep until 02:00

Outline

- Review of TBI Definitions
- Sleep Complaints and TBI
- Evaluation
  - Subjective
  - Objective
- Co-Morbidities
- New Paradigms
  - Neuroplasticity
  - Possible Long-Term Issues
- Summary





Evolution of Diagnosis of Concussion/mTBI

- Early 80s: mild head injury criteria
  - GCS score 13-15, LOC < 20 min
  - Hospitalization < 48 hrs, No neuroimaging evidence

- 1993: Term mild traumatic brain injury established by special committee of American Congress of Rehabilitation Medicine (ACRM)
  - Added alteration of Cs at time of incident
  - PTA < 24 hrs

- CDC and WHO: use terms concussion and mild TBI interchangeably

- 2009 Consensus Statement definition
  - "Complex pathophysiological process affecting the brain, induced by traumatic biomechanical forces"

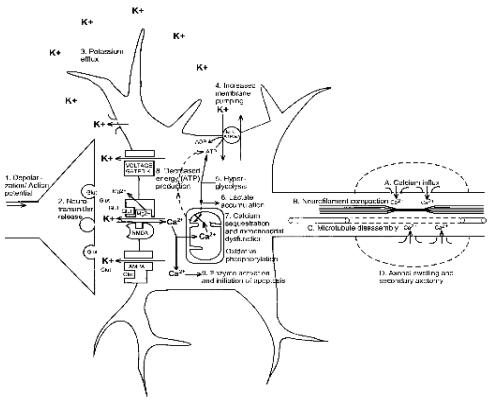


Figure 2. Neurometabolic cascade following traumatic injury. (1) Nonspecific depolarization and initiation of action potentials. (2) Release of excitatory neurotransmitters (EAAs). (3) Massive efflux of potassium. (4) Increased activity of membrane ionic pumps to restore homeostasis. (5) Hyperglycolysis to generate more adenosine triphosphate (ATP). (6) Lactate accumulation. (7) Calcium influx and sequestration in mitochondria leading to impaired oxidative metabolism. (8) Decreased energy (ATP) production. (9) Calpain activation and initiation of apoptosis. A, Axolemmal disruption and calcium influx. B, Neurofilament compaction via phosphorylation or sidearm cleavage. C, Microtubule disassembly and accumulation of axonally transported organelles. D, Axonal swelling and eventual axotomy. K^+, potassium; Na^+, sodium; Glut, glutamate; Mg^{2+}, magnesium; Ca^{2+}, calcium; NMDA, N-methyl-D-aspartate; AMPA, d-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid.

TBI Classification

Criteria	Mild	Moderate	Severe
Structural imaging	Normal	Normal or abnormal	Normal or abnormal
Loss of Consciousness (LOC)	0–30 min	> 30 min and < 24 hours	> 24 hrs
Alteration of consciousness/mental state (AOC) *	a moment up to 24 hrs	> 24 hours. Severity based on other criteria	
Post-traumatic amnesia (PTA)	0–1 day	> 1 and < 7 days	> 7 days
Glascow Coma Scale (best available score in first 24 hours)	13-15	9-12	< 9

* Alteration of mental status must be immediately related to the trauma to the head. Typical symptoms would be: looking and feeling dazed and uncertain of what is happening, confusion, difficulty thinking clearly or responding appropriately to mental status questions, and being unable to describe events immediately before or after the trauma event.

Severity level has prognostic value, but does not predict the patient's ultimate level of functioning.

Sleep and TBI Intertwining Issues

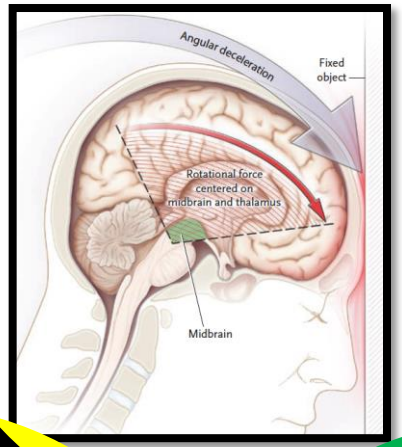
- Sleep complaints are one of the most common complaints and symptoms following TBI
  - Sleep complaints prevalent in general population

- Different systems for clustering post-concussion symptoms
  - CDC: 4 clusters
    - Cognitive, Physical, Emotional, Sleep
  - ACRM: 3 clusters
    - Cognitive, Physical, Emotional
    - Sleep complaints considered within Physical Sx cluster

- Possible pre-morbid risk factor
  - Sleep disorders increase risk for MVA
  - MVA #1 cause for TBI/concussion
  - Decreased athletic reaction time and performance

Concussion: Signs & Symptoms

<u>Somatic Symptoms</u>
Headaches
Nausea
Dizziness/Poor Balance
Light/Sound Sensitivity



<u>Cognitive Symptoms</u>
"Fogginess"
Cognitive Fatigue
Inattention
Memory Deficits

<u>Sleep Disturbance</u>
Insomnia
Fragmented Sleep
Hypersomnia
Hyposomnia

<u>Mood</u>
Irritability
Lability
↓Frustration Tolerance
Sadness
Anxiety

Slide from Dr. Donna Broshek

Limitations in Current Research on Sleep and TBI

- Correlating sleep symptoms with injury
  - Location of damage
  - Severity of injury
- Studies do not clearly stratify by time following injury (acute vs. chronic)
- Biological aspects of co-morbid psychological/stress conditions has not been fully explored
- Contribution of other co-morbid injuries and contributing/modifying factors (e.g. pain and medications)
- Relationship between impaired sleep and other post TBI symptoms
- Lack of understanding pre-morbid issues

Ways to Evaluate Relationship Between TBI and Sleep

- Subjective reports
- Objectively measured sleep disturbance
  - Polysomnography (EEG and respiratory parameters)
  - Multiple Sleep Latency Test (MSLT)
  - Actigraphy (sleep-wake rhythms)
- Circadian rhythm parameters
- Other neurophysiologic / neuropsychological parameters

Prevalence of Sleep Disturbance after TBI Examples of Different Lenses

- Prevalence of sleep disturbance 42-70%
  - Fichtenberg et al., 2002; Makley et al., 2008

- 3 mos post TBI (Castriotta et al., 2007)
  - Abnormal PSG in 47%
    - Architecture changes: decreased N2, increased SWS
  - Abnormal MSLT in 25%
    - No correlation between ESS and MSLT

- In 1st 3 mos, acute post-TBI anxiety disorder most consistent significant risk factor associated with worsening sleep status (Rao et al., 2008)

- Abnormalities in acute sleep EEG spectral analysis noted in TBI patients (not noted on PSG) (Rao et al., 2011)

Subjective Sleep Complaints Following TBI (All Severities)

- Excessive daytime somnolence (approx 50%)
- Insomnia (approx 33%)
  - ½ with sleep onset insomnia (Increased latency)
    - Associated with higher anxiety scores
  - ½ with sleep maintenance insomnia (increased awakenings)
    - Associated with higher depression scores
- Parasomnias (approx 25%)
    - Most common is REM Behavior Disorder (Verma, Anand, & Verma, 2007)
    - Theory: Damage to brainstem mechanisms (peri-locus ceruleus area sending excitatory impulses to nucleus reticularis magnocellularis in medulla)
- Multiple replicated studies illustrating subjective complaints

Mild TBI and Subjective Insomnia

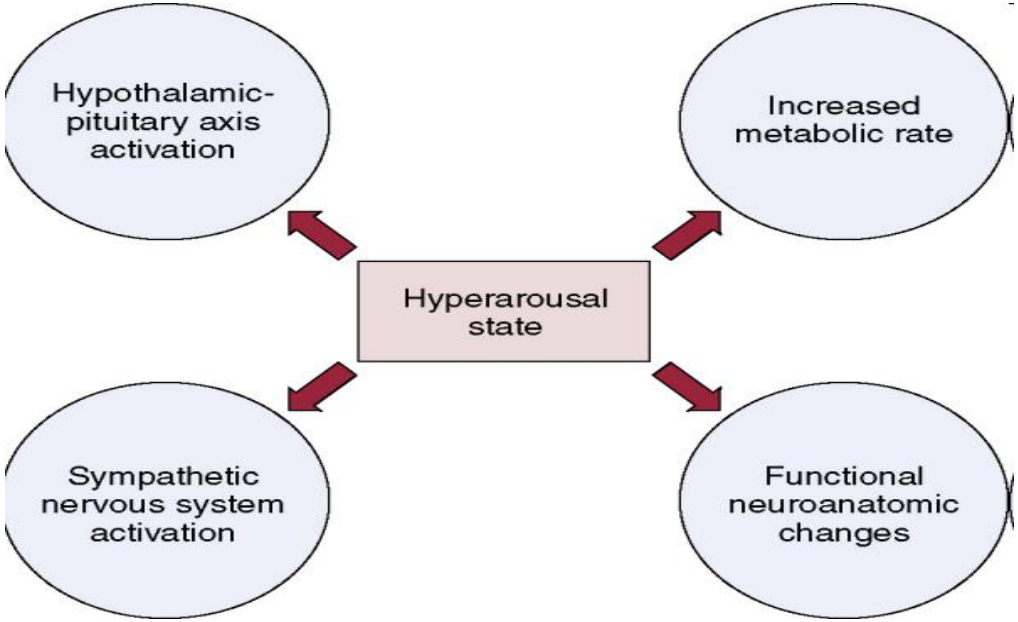
- On subjective reports, mTBI more associated with insomnia than severe forms of TBI
- Can be reported acutely or chronically (> 3 mos)
- High symptom load acutely provides higher risk for persistence
- With objective evaluations, severity of insomnia is over-estimated
  - Consistent with overall insomnia literature
  - Possibly related to hyper-arousal effects on perception

mTBI and Insomnia Pathophysiology Theories

- More diffuse injuries (diffuse axonal injury) that occur in mTBI lead to impairment in global functioning (e.g. arousal) more so than acute or focal traumas.
  - May contribute to EEG observations

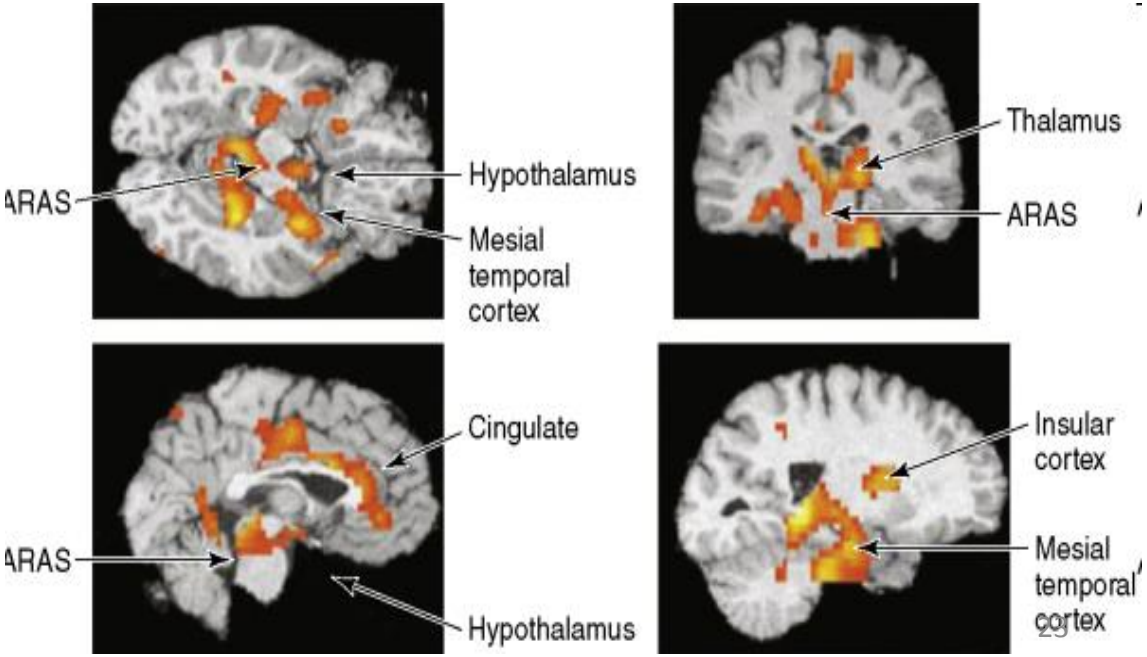
- Dysregulation of shifting or maintaining sleep states?
  - Different states involve activation of different parts of the brain

- Awareness –
  - Moderate-severe TBI may be less aware of deficit
  - Mild TBI may be hyper-aware
    - Possibly driven by post-concussive anxiety



Hyper-Arousal in Insomnia

Images from Atlas of Sleep Medicine
Kryger et al., 2014



TBI and Objectively Measured Sleep Disturbance

- Harder to Identify due to confounding factors
  - Uses diagnostic tools such as polysomnogram (PSG) and Multiple Sleep Latency Test (MSLT) each of which has limitations
    - These studies often lead to diagnoses based on findings on test
- Difficult to clarify if disorder seen on test is pre-morbid vs. due to injury
- First Night Effect observed in sleep labs
- Studies have described
  - Sleep disorders identified on diagnostic sleep tests
  - Observations on EEG trends

NICoE Data on SDB

- 94 patients evaluated

- Sleep disordered breathing in 41.5% (n=39)
  - Mean BMI with SDB: 29.8 +/- 3.6
  - Mean BMI of non-SDB patients: 26.8 +/- 3.4

  - TBI alone: 43.6%
  - PTSD and TBI: 46.2%
  - PTSD alone: 7.7%

Observational Studies from PSG /MSLT Abnormal Studies in 46% Leading to Diagnosis Studies did not Stratify TBI Severity

- Obstructive sleep apnea – 23%
  - Observed in more obese patients
  - 4-9% in general population
- Periodic limb movements of sleep – 7 to 25.4%
  - 5% in general population
- Post-traumatic hypersomnia
  - May be related to damage to hypocretin production
- Objective evidence of excessive daytime somnolence in 25% (MSLT < 10 minutes)
  - No correlation between subjective report on Epworth Sleepiness Scale and MSLT results
  - Implication: lack of awareness
- Narcolepsy – 6%

Hypersomnia in TBI

- A common complaint
- More prominent than in injuries involving head than in injuries not involving head at 1 month following injury
- Hypersomnolence improves in many but 25% may have persistent symptoms at 1 year
- Severity of injury correlates with severity of hypersomnia and risk of persistence

Hypersomnia in Severe TBI

- 15 months after TBI injury (Guilleminault et al, 2000)
  - 98% reported EDS
    - 82% had MSLT SL < 10 minutes
    - 32% had SDB
      - Note: TBI has been reported to worsen SBD
- Risk factors
  - Coma > 24 hours, neurosurgical intervention, pain, skull fracture
- Injury to posterolateral hypothalamus provides physiologic basis

TBI Endocrine Pathophysiology

- Up to 50% of TBI have impaired neuroendocrine function
- Of these, 20% have a combination of 2 or more deficiencies
  - Many are transient
  - Panhypopit: no recovery when ID acutely
- Most common: growth hormone deficiency
  - 15% of subjects (per glucagon stim testing)
  - Best clinic screen: IGF-1
- Hypocretin (Known to be reduced in narcolepsy)

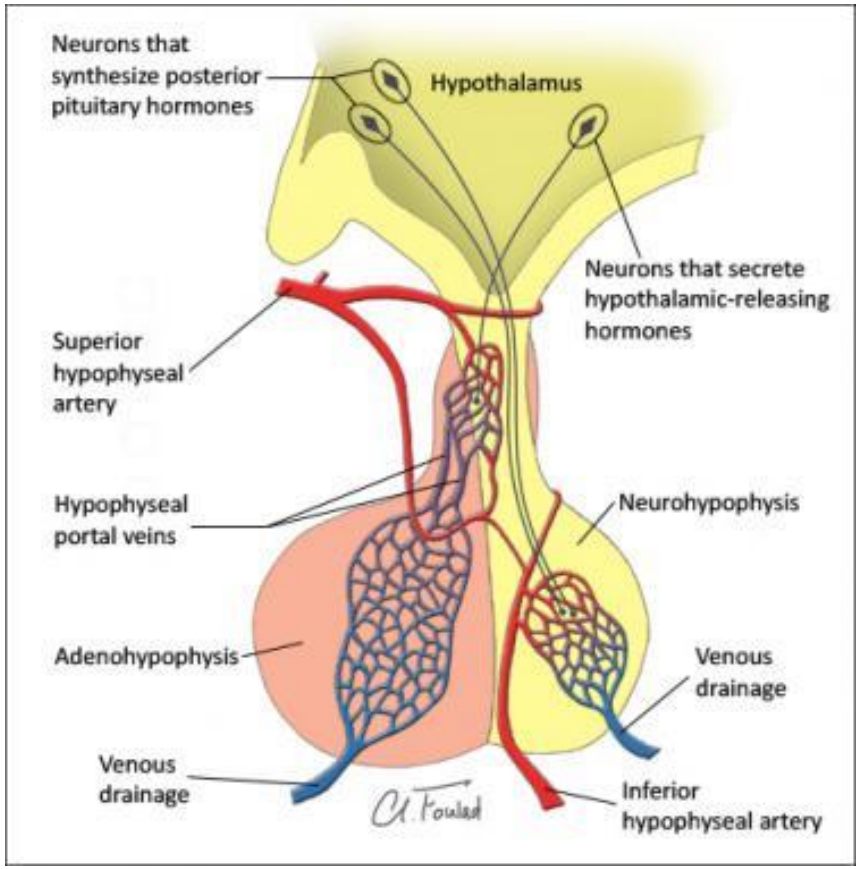
  -- Hypocretin-1: Low CSF levels in 95% moderate-severe TBI (Baumann et al. 2005)

  Decreased acutely with transient hypothalamic dysfunction

  Many TBI patients normalize at 6 months
- Possible state change regulation dysfunction

TBI-Related Pituitary Dysfunction

- Hierarchy of vulnerability to trauma
  - Most vulnerable
    - Somatotrophs, gonadotrophs
    - Tend to be located more in lateral wings
    - Supplied primarily by long, hypophyseal portal system
  - More resilient
    - Corticotrophs, thyrotrophs
    - Located more in central portion of gland
    - Supplied primarily by short, hypohyseal portal systems

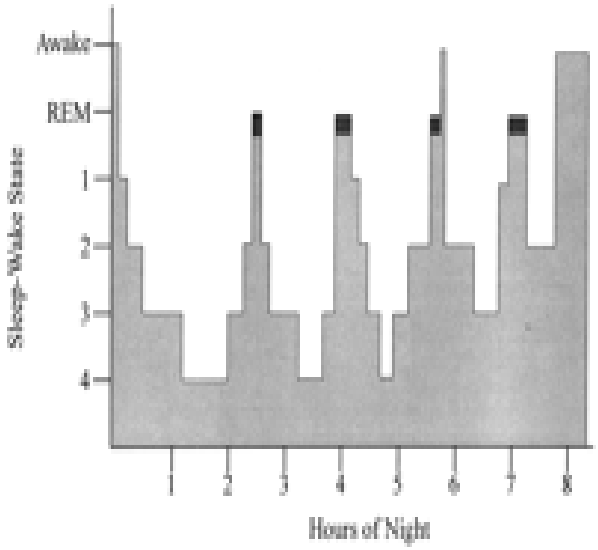


hSource: Medscape

Sleep Architecture Observation

- Moderate-severe
- Increased slow-wave sleep in TBI after controlling for depression and anxiety scores
- Mild TBI
- Decreased REM
- Higher N1 and N2

  (Schreiber et al., 2008)

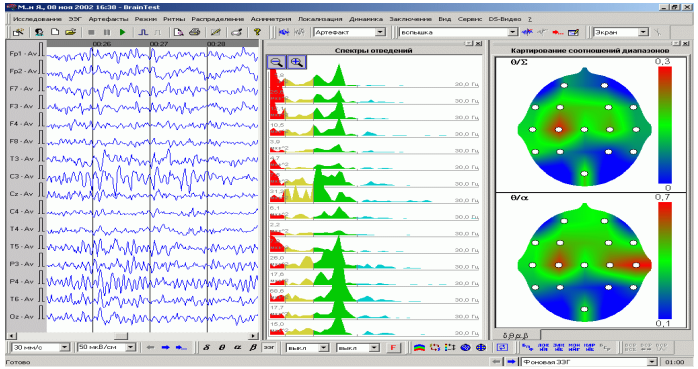


Normal Sleep

Specialized EEG Observations

- Spectral EEG in athletes with concussion
- More delta activity and less alpha activity during wakefulness
- Possible implication for waking EEG in prognosis due to association with sx

  (Gosselin et al., 2009)



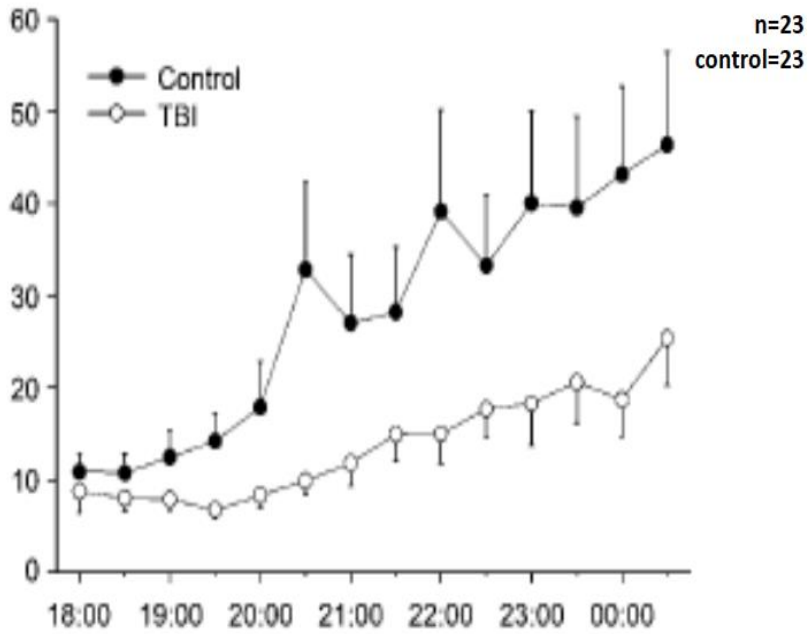
- Quantitative EEG
- EEG delta power thought to correlate with frontal lobe executive function
- Correlates with homeostatic process

TBI and Circadian Changes

- Sleep disturbance following TBI may be associated with alterations in timing and rhythm of sleep
  - Mismatch between biological sleep-wake schedule and desired 24-hour environmental and social schedule

Circadian Effects of TBI

Decreased Evening Melatonin in TBI



- Associated altered rhythm/timing of melatonin secretion and body temperature

  Melatonin: evening production reduced (Shekelton et al., 2010)

Circadian Rhythm Disturbances and TBI

- Delayed sleep phase syndrome
  - Often misinterpreted as insomnia
  - Limited research
    - One study described 15 of 42 patients (36%) with insomnia following mTBI were more properly diagnosed with CRSD
      - Ayalon et al., 2007
    - One recent study of 23 patients described decreased melatonin release (DLMO)
      - Shekelton et al., 2010
    - Issue: Pre-morbid finding vs. result of injury
  - General population with CRSD in context of insomnia c/o: 7-10%
- Free-running: Described in case report of blast patient with associated eye injuries

Objective Sleep Disturbance and Mild TBI Re-evaluating Evidence by Stratifying Severity

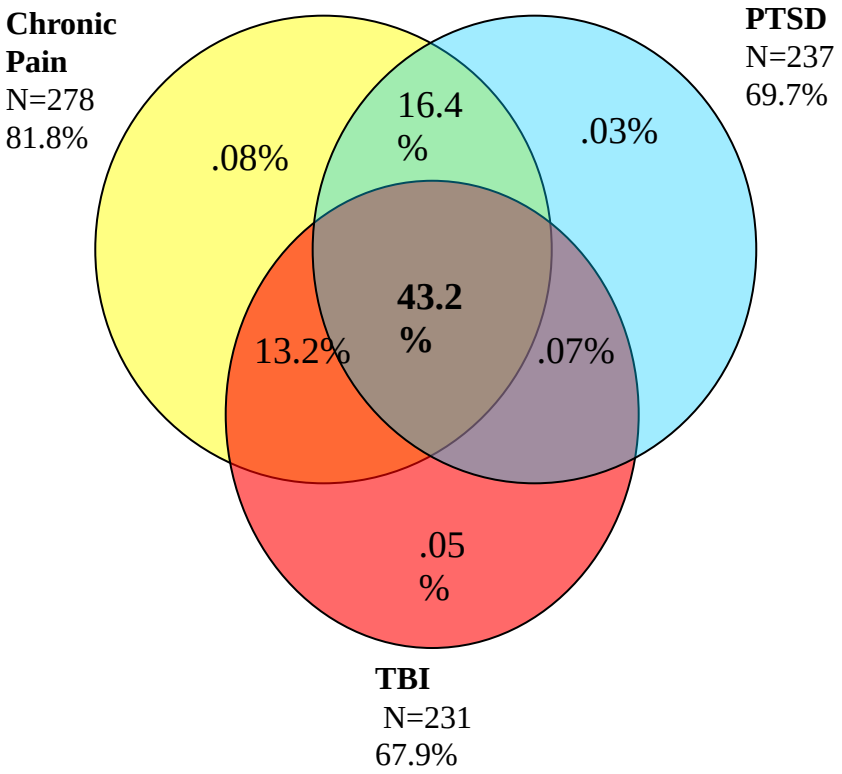
- Objective evidence is most equivocal of reviewed outcome measures in mild TBI
  - Despite majority of subjective complaints

- Further challenges with the literature
  - Small sample sizes in most studies
  - Variability in age ranges across studies
  - Samples with mixed severity of injury
  - Not specific for mechanism (i.e. athletic)
  - Lack of advanced imaging or EEG correlation

Challenge of Co-Morbidities

- Pre-existing primary sleep disorders
- Psychological / Psychiatric
  - Pre-existing
  - Associated post-concussive symptom

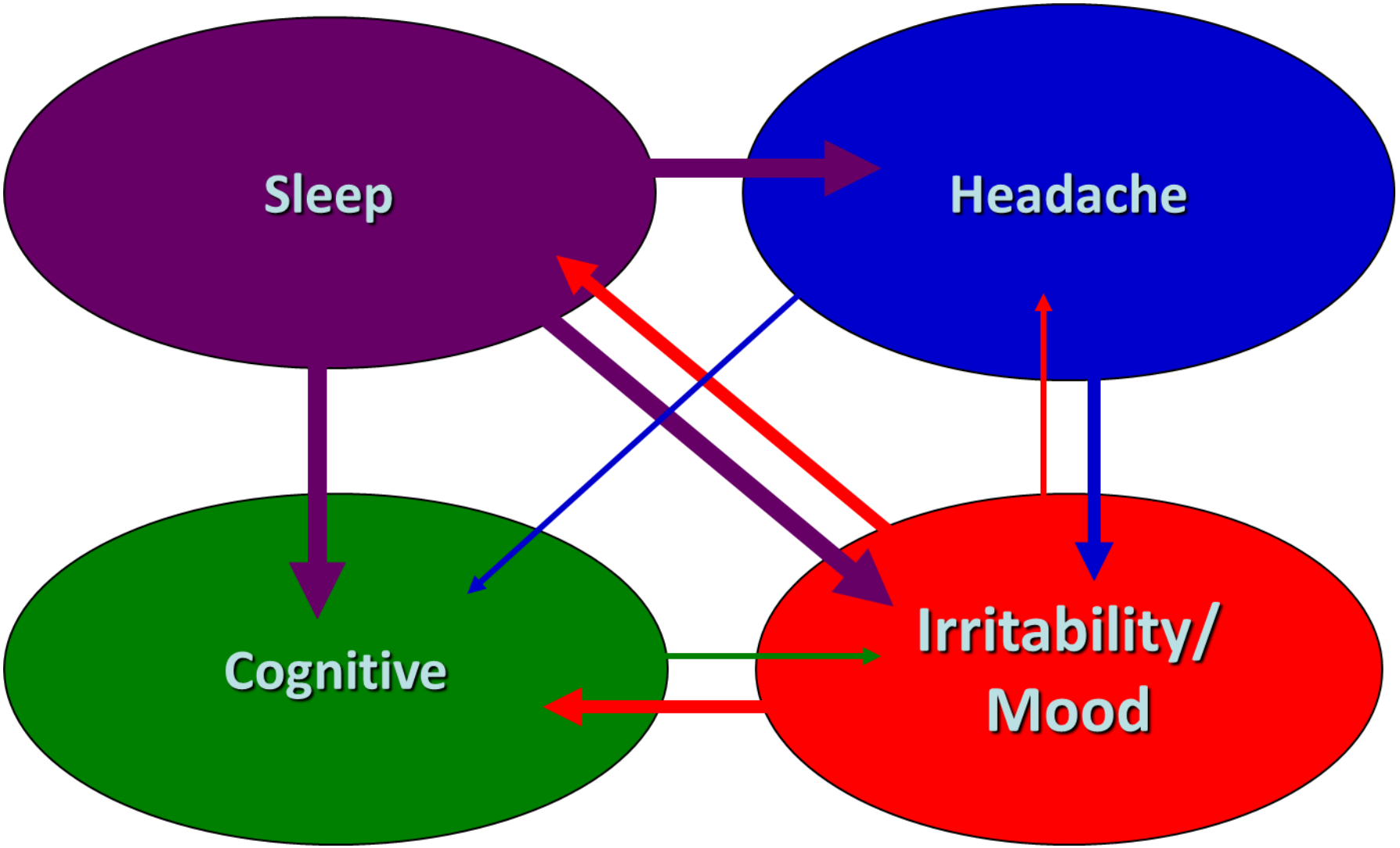
Figure 1. Relative distribution of the "Polytrauma Triad" in a sample of 340 OEF/OIF veterans evaluated at the VA Boston Polytrauma Network Site



Multifactorial Issues for Sleep Complaints in TBI

- Result of trauma
- Secondary to medical problems
- Pain
- Neuropsychiatric disturbances
- Medication effects

- May be different processes with acute TBI sx and chronic symptoms


Sleep
Headache
Cognitive
Irritability/
Mood

Meta-analysis of sleep deprivation effects on cognition

- 70 studies comprising 1,533 subjects
- SD could not exceed 48h
- **Attentional** tasks most impaired following SD (effect sizes -0.762 for lapses, -0.732 for reaction time)
- Moderate effect sizes showing impairment in **working memory** and **complex attention**
- No significant effect of SD on **reasoning**

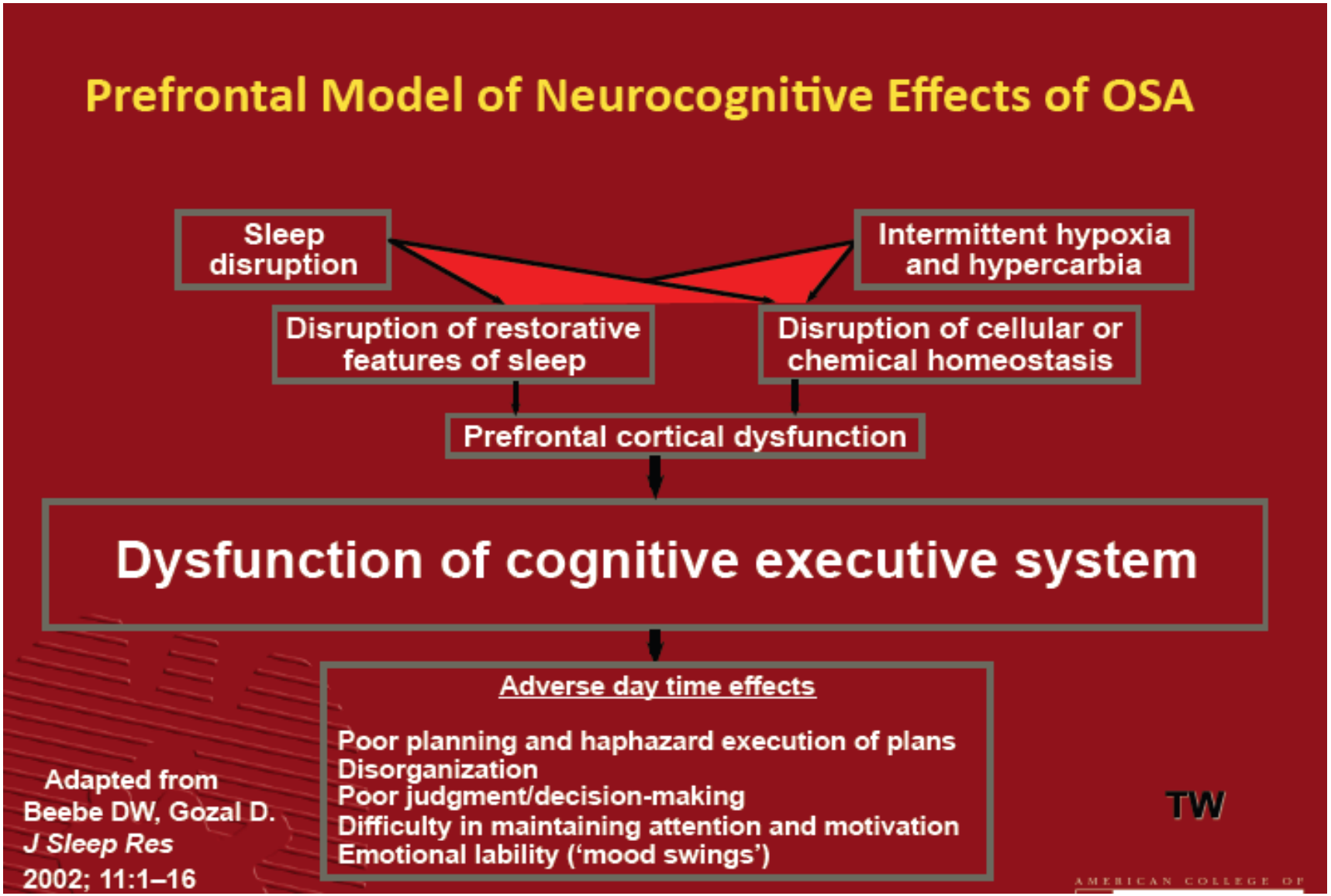
Lim J and Dinges DF, Psychological Bulletin (2010), 136:375-389

Effects of sleep apnea on cognition

Association of Sleep Disordered Breathing and Cognitive Deficit in *APOE* ε4 Carriers

Compared to participants without sleep apnea, those with moderate-severe sleep apnea had:

- **Reduced verbal memory**
  similar "effect" as 10 fewer years education
- **Reduced oral word fluency**
  similar "effect" as 4 fewer years education

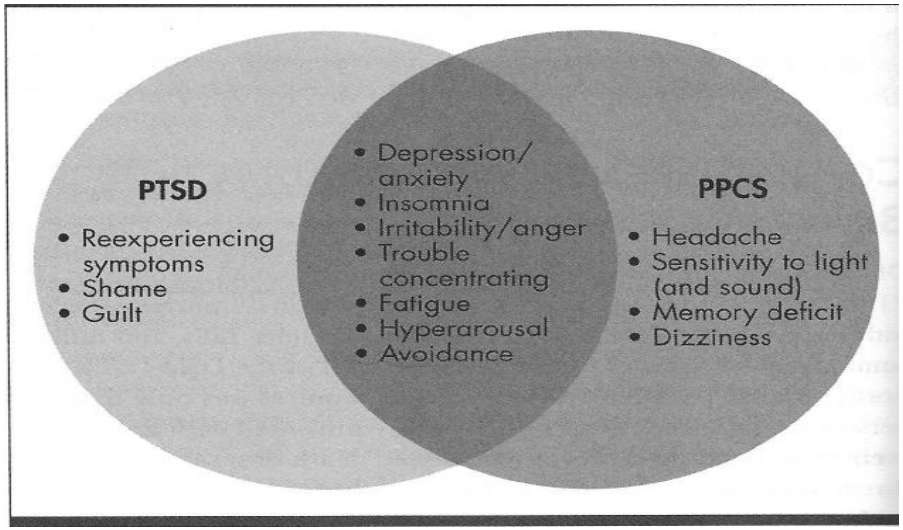


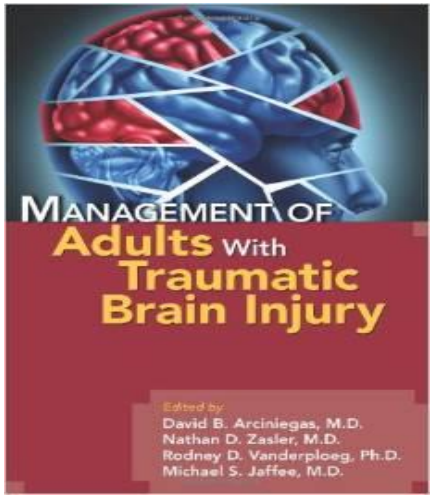
ACCP Review

Difficult to distinguish effects of TBI and OSA on neuropsychological testing due to common pathway of executive system

Challenge of Psychiatric/Post-Concussive Co-Morbidities

- Sleep disturbances of co-morbid psychiatric disorders to include PTSD
- Synergistic aspects of TBI and psychiatric co-morbidity
- Independent relationship of TBI and psychiatric disorders to obstructive sleep apnea?





Sleep Disorders and PTSD

- Insomnia – reported in 70 – 91 %

- Nightmare disorder reported in 19-71%
  - Image rehearsal therapy
  - Prazosin

- Periodic limb movements of sleep
  - May be sign of increased arousal
  - May contribute to awakenings and insomnia

- Obstructive sleep apnea: Found on PSG studies
  - 69% of sample of 105 Vietnam veterans (Yesavage et al., 2012)
  - 73% of random sample of current AD servicemen w/ PTSD
  - Difficulty tolerating CPAP
    - Adherence 41% compared to 70% in control group (El-Solh et al, 2010)
    - CPAP proposed as possible treatment for PTSD-related insomnia (Krakow et al., 2002)

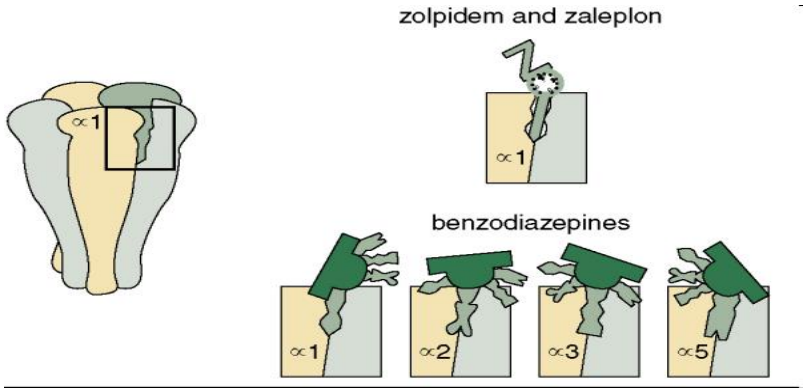
Treatment of Sleep Complaints in Setting of TBI

- Target symptom approach
- Insomnia
  - Cognitive-behavioral treatment of insomnia –CBTI
    - Limited literature on efficacy in TBI population
    - Case study: Ouellet and Morin
    - Main recommendation in DoD/VA guidelines and Ontario Neurotrauma Foundation
  - Medications (prescription and OTC) remain most common and accessible
- Circadian rhythm disorders
  - Exogenous melatonin
  - Phototherapy
- Hypersomnia (primarily for moderate-severe TBI)
  - Modafanil / Armodafanil
  - Stimulants
- OSA
  - CPAP

Effect of Sleep Meds on Cognitive Recovery

Larson & Zollman, 2010

- Use of benzodiazepines is contra-indicated
- Adverse effect on cognition
- Adverse effects on neuroplasticity
  - Thought to not be as persistent with atypical GABA agonsist ("Z-drugs")
- Recommended trazodone, melatonin, ramelteon (Melatonin agonist)



Role of Medications

- **VA/DoD Clinical Practice Guideline for TBI**
  - Ambien (max duration: 10 days), trazodone, Elavil
  - Subsequent dosing modification from FDA 2013

- **Updated DoD Guidance 2014:**
  - Allowed option of other Z-drugs no more than 2 weeks at a time and for no more than 30 days total
  - Do not recommend antihistamines, antipsychotics
  - Consider prazosin for co-morbid PTSD

Ontario Neurotrauma Guidelines

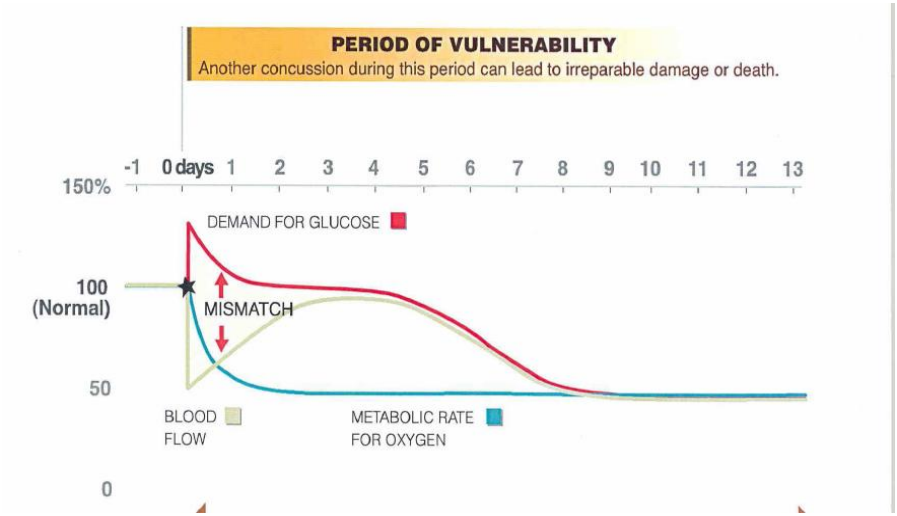
- Medications should be used on a short-term basis only.
- Medications that can be used include trazodone, mirtazapine, and tricyclic antidepressants (e.g., amitryptyline).
- Benzodiazapines should generally be avoided; however, newer non-benzodiazepine medications (e.g., zopiclone, eszopiclone) may have fewer adverse effects and may be considered for short-term use.
- Other non-pharmacologic treatment options that have been found to be useful in the treatment of insomnia include:
- Daily supplements of magnesium, melatonin, and zinc.
- Consider other interventions such as acupuncture, exercise, and mindfulness-based stress reduction.

Ontario Neurotrauma Foundation
Fondation ontarienne de neurotraumatologie

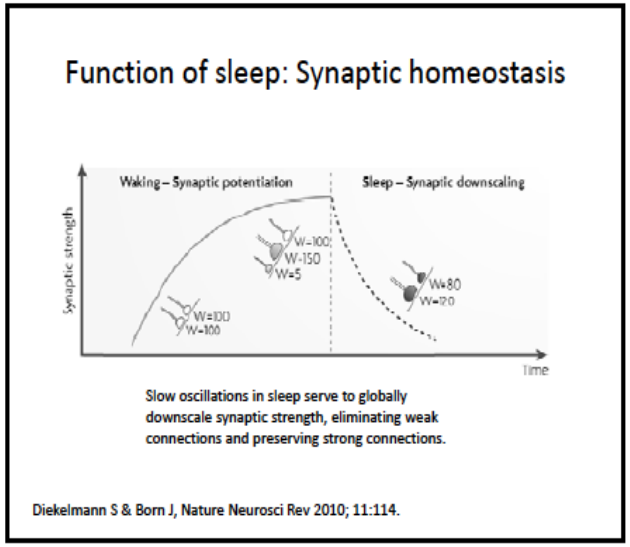
Treatment Paradigms

- Target symptom approach
- Enhance neuroplastic recovery
  - Concussion pathophysiology
    - Initial metabolic storm
    - Subsequent neurometabolic energy mismatch

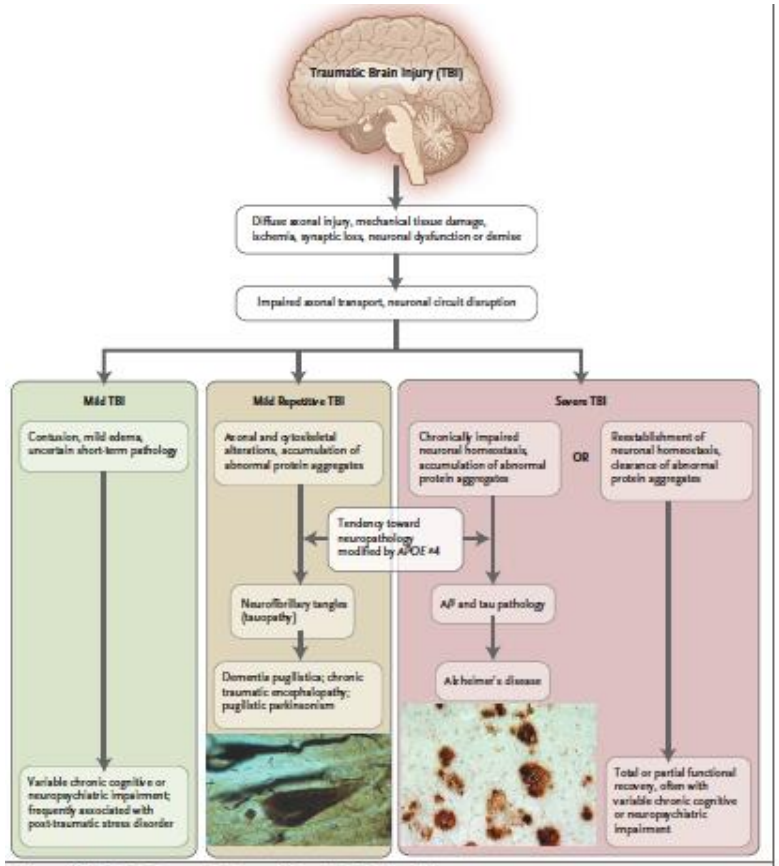
      80% of energy consumed by wake synaptic activity



Giza & Hovda, 2001



Possible Role of SD in Recurrent mTBI and Long-term Effects?



Spectrum of Pathologic Features and Outcomes of Traumatic Brain Injury (TBI).
In the left inset, Bielschowsky silver stain shows intraneuronal and extracellular neurofibrillary tangles in temporal cortex from a retired boxer with dementia pugilistica.[1] The right inset shows diffuse Aβ plaque deposits in temporal cortex from a subject who sustained severe TBI.[2]

DeKosky et al., NEJM, 2010

Chronic Traumatic Encephalopathy

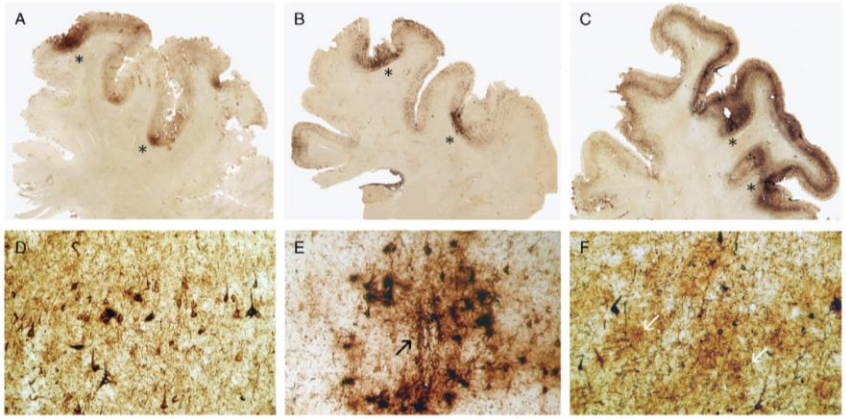


FIGURE 2. (A–C) Whole-mount 50-μm coronal sections of superior frontal cortex from Case A **(A)**, Case B **(B)**, and Case C **(C)** immunostained for tau with monoclonal antibody CP-13 showing extensive immunoreactivity that is greatest at sulcal depths (asterisks) and is associated with contraction of the cortical ribbon. **(D–F)** Microscopically, there are dense tau-immunoreactive neurofibrillary tangles (NFTs) and neuropil neurites throughout the cortex, Case A **(D)**, Case B **(E)**, and Case C **(F)**. There are focal nests of NFTs and astrocytic tangles around small blood vessels **(E**, arrow**)** and plaquelike clusters of tau-immunoreactive astrocytic processes distributed throughout the cortical layers **(F**, arrows**)**.

CTE: considered a tau accumulation neurodegeneration

McKee et al, J Neuropathol Exp Neurol, 2009

Why Treat Insomnia?

2000s; Promotes better medical and or psychiatric health

Insomnia can precipitate, exacerbate or prolong comorbid conditions, thereby treatment of insomnia may improve comorbidities

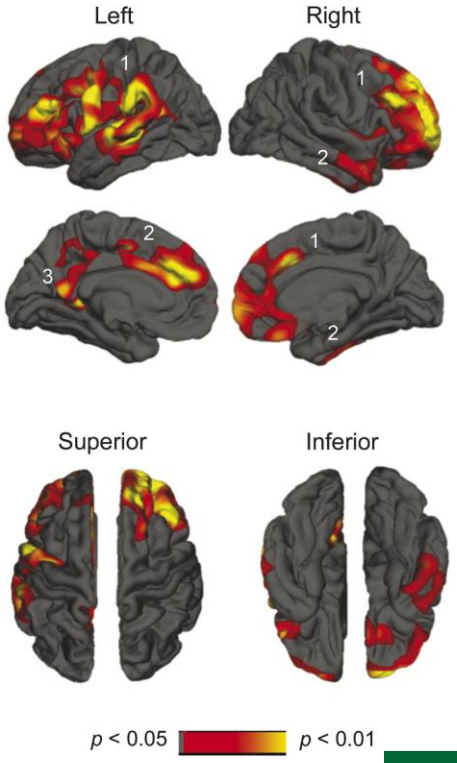
Biological Psychiatry
Official Journal of the Society of Biological Psychiatry

- **Smaller hippocampal volumes correlated with poor sleep quality**

- Reduced orbitofrontal and parietal gray matter in chronic insomnia: A voxel-based morphometric study
  - Altena, et. al.
  - Volume 67, Issue 2, Pages 182-185 (15 January 2010)

- Poor sleep quality is associated with increased cortical atrophy in community-dwelling adults
  - Sexton, et. al.
  - Neurology, Volume 83, Sept 2014

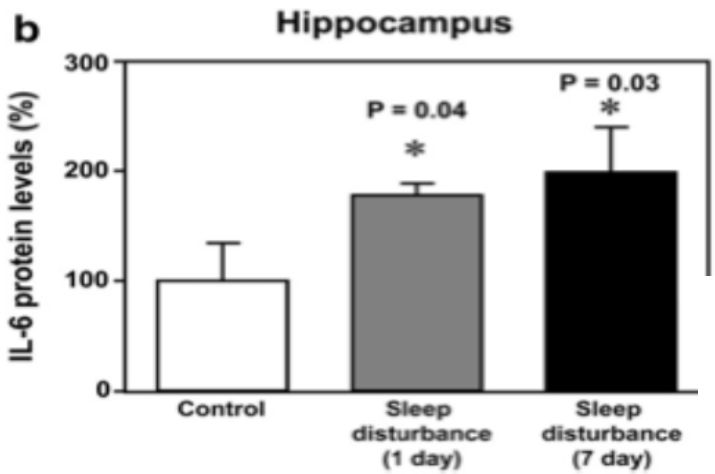
  - Increased rate of atrophy within widespread frontal, temporal, and parietal regions in longitudinal analyses



NEUROLOGY®

Effects of Chronic Sleep Loss (Animal Study)

Neuroinflammation



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control=6

Microglia Activation

n=6
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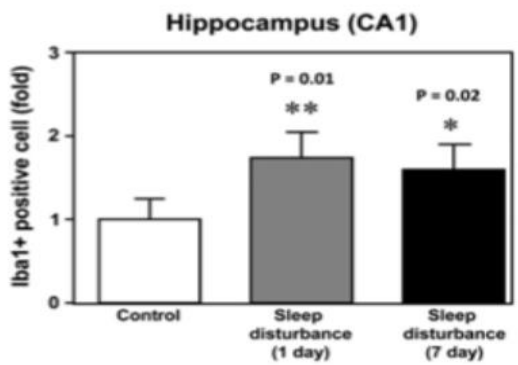
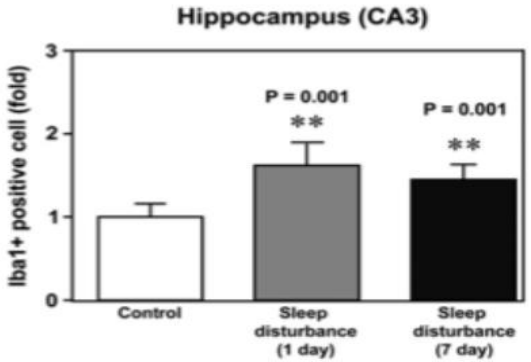


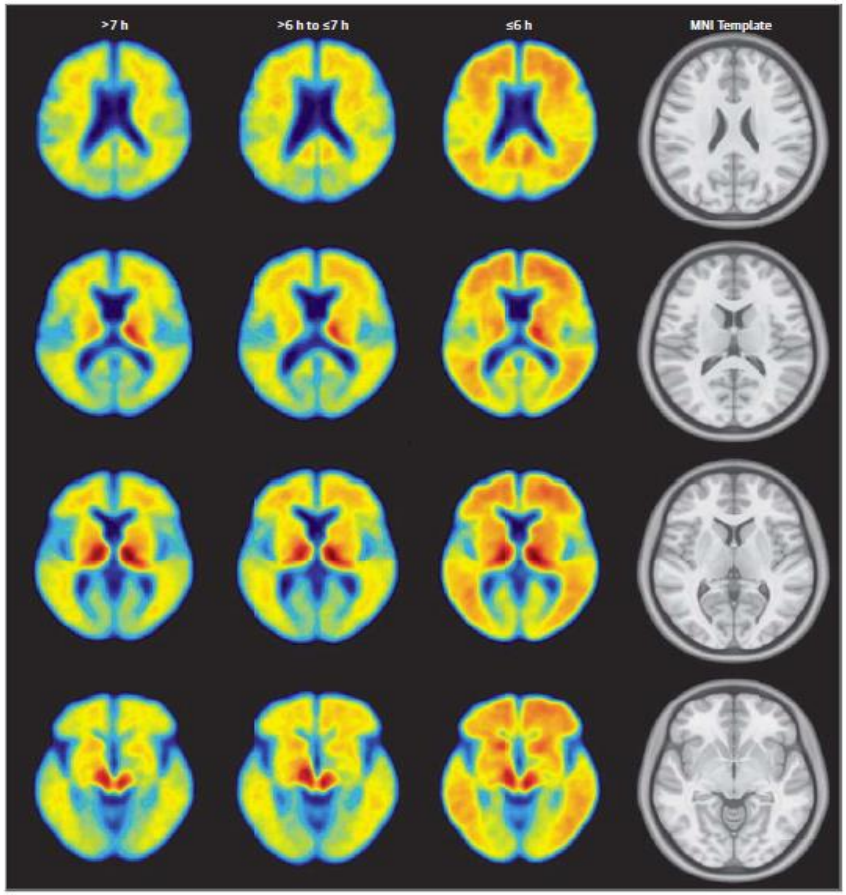


Hippocampus more susceptible than cortex

Zhu, et al., Neurobiol Dis, 2012

Does post TBI SD Relate to Degeneration Findings in AD?

Figure. Unadjusted Distribution Volume Ratios (DVRs) of Carbon 11–Labeled Pittsburgh Compound B Positron Emission Tomography Images by Sleep Duration



JAMA Neurology
Formerly *Archives of Neurology*

ORIGINAL CONTRIBUTION

Sleep Quality and Preclinical Alzheimer Disease

Yo-El S. Ju, MD; Jennifer S. McLeland, MSW, MA; Cristina D. Toedebusch, BS; Chengjie Xiong, PhD; Anne M. Fagan, PhD; Stephen P. Duntley, MD; John C. Morris, MD; David M. Holtzman, MD

Original Investigation

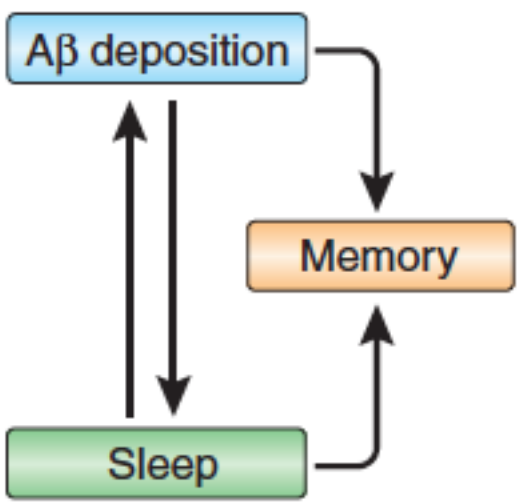
Self-reported Sleep and β-Amyloid Deposition in Community-Dwelling Older Adults

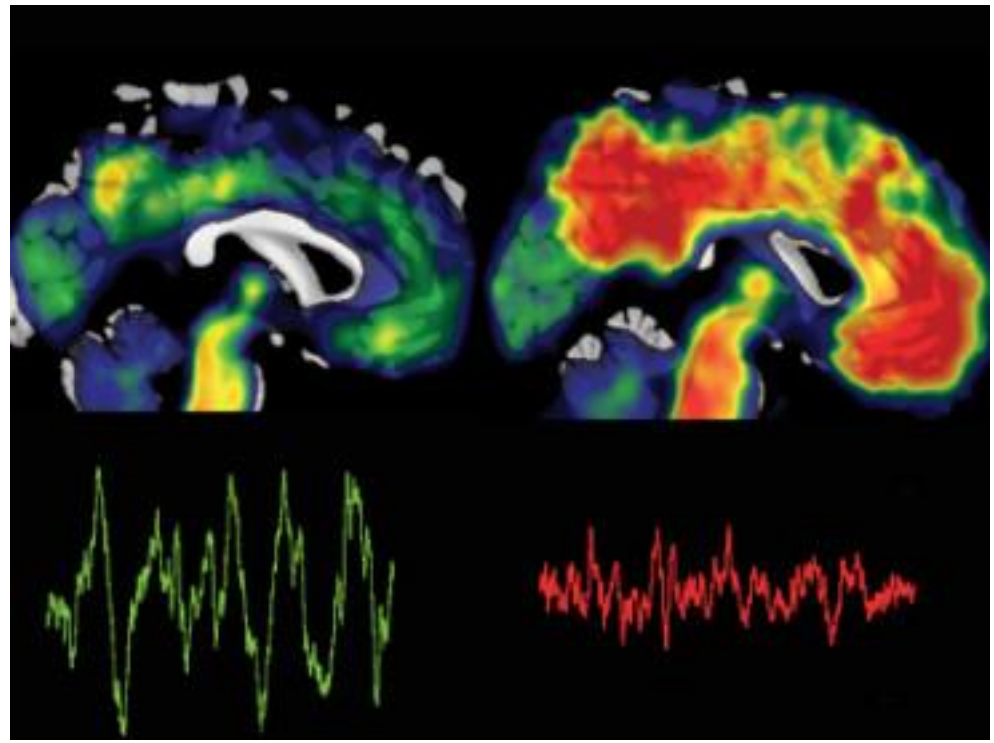
Adam P. Spira, PhD; Alyssa A. Gamaldo, PhD; Yang An, MS; Mark N. Wu, MD, PhD; Eleanor M. Simonsick, PhD; Murat Bilgel, BS; Yun Zhou, PhD; Dean F. Wong, MD, PhD; Luigi Ferrucci, MD, PhD; Susan M. Resnick, PhD

β-amyloid disrupts human NREM slow waves and related hippocampus-dependent memory consolidation

Bryce A Mander[1], Shawn M Marks[2], Jacob W Vogel[2], Vikram Rao[1], Brandon Lu[3], Jared M Saletin[1], Sonia Ancoli-Israel[4], William J Jagust[2,5] & Matthew P Walker[1,2]

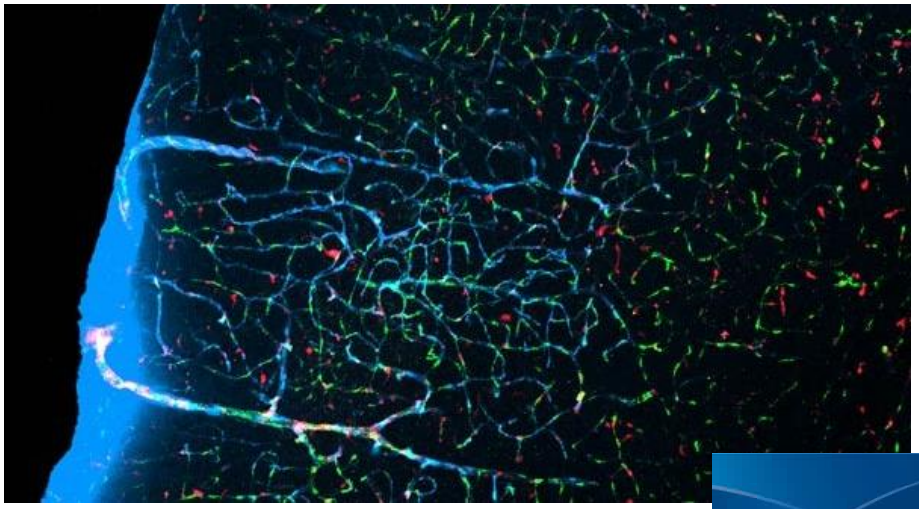
nature neuroscience





Could this affect possible neuroplastic recovery?

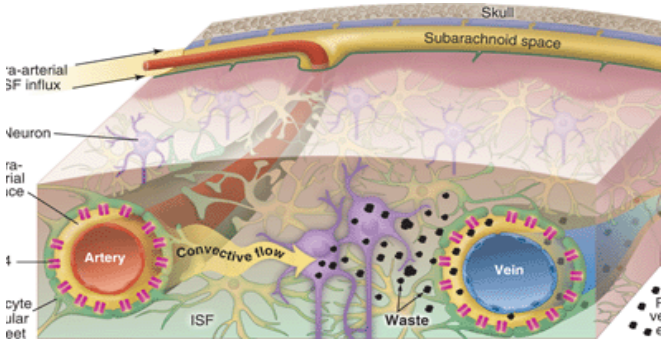
Sleep as a “Brain Washer”



http://scienceon.hani.co.kr/files/attach/images/73/206/126/00brainwash.jpg

Role of Glymphatics

Amyloid found as acute trauma marker. Does lack of clearance have recovery or long-term effect?



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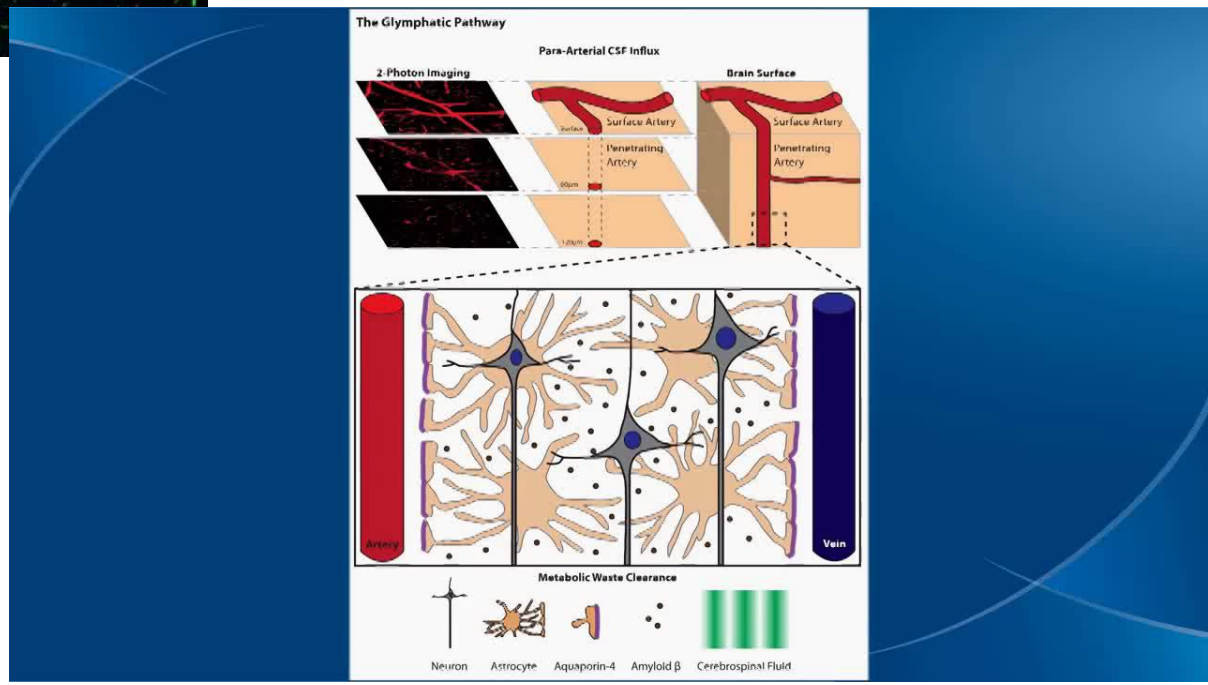

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Take-Home Messages

- Sleep issues and TBI are very intertwined
  - Co-morbidities
- mTBI has more sleep complaints
  - Usually insomnia
- Delayed circadian phase can present as insomnia
- Prevalence of post-injury hypersomnia more of an issue in moderate-severe TBI
  - May have endocrine basis with decreased hypocretin
- Consider sleep screening in TBI patients with sleep c/o
- More research is needed to further guide evaluation and management and explore newer paradigms

1. Develop trials registry
2. Improve tools/identify patient-centered outcomes
3. Standardize assessment criteria for trials
4. Treatment of hypersomnia / hypocretin deficiency
   - large RCT w/ modafinil/armodafinil/pipeline
   - target functional outcomes
5. Stratify by severity – study mTBI separately
6. Stakeholder follow-up

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Questions?

- Please submit your questions now via the question box located on the left side of the screen.

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- VHA and all other federal partners:
  - Erica Jackson: Erica.Jackson2@va.gov

Announcement

- CANCELLED: Grand Rounds January 18, 2017
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