



2017 Traumatic Brain Injury Conference

February 10, 2017 | *Marriott Eaton Centre, 525 Bay Street, Toronto*



Sleep and Wake Disturbances following TBI: Current Knowledge and Best Practice

Overview & Learning Objectives

Sleep, Wakefulness and TBI:

- » Epidemiology
- » Pathophysiology and evolution across recovery
- » Types of sleep disorders

Why Does this Matter? Introduction to Normal Sleep:

- » Characteristics
- » Developmental changes across the lifespan
- » Sleep need
- » Consequences of sleep loss, deprivation & disturbed sleep

Sleep, Wakefulness and TBI; Implications for Clinical Practice:

- » Sleep and Recovery
- » Assessment
- » Management





Sleep, Wakefulness and TBI

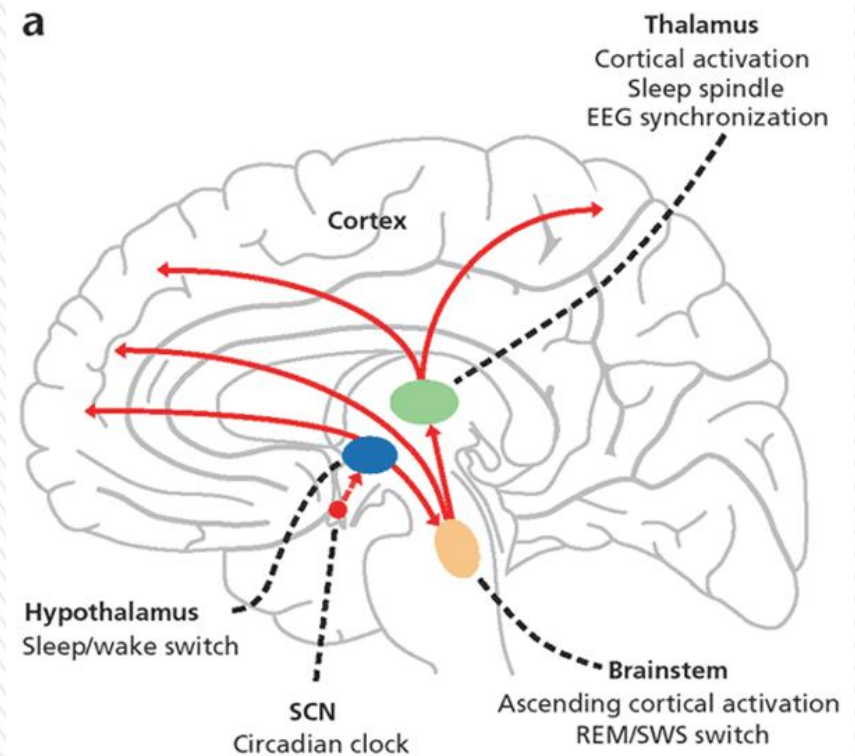


- » Individuals with chronic TBI across all levels of severity from concussion – moderate-severe injuries, experience wide-spread, objective sleep deficits Grima et.al. J Clinical Sleep Medicine 2016
- » Greater than 50% of those with TBI suffer from sleep disturbance, and 25-29% have a diagnosed sleep disorder Mathias & Alvaro Sleep Medicine 2012
- » 30-70% of mTBI patients experience sleep problems Singh et.al. Pediatric Neurology 2016

Epidemiology



» Brain regions and systems regulating arousal, alertness, attention, & sleep i.e. basal forebrain, anterior reticular activating system & Suprachiasmatic nucleus of the hypothalamus are highly vulnerable to the biomechanical mechanisms of traumatic brain injury; acceleration-deceleration and rotation



Pathophysiology



- » Begins in the acute stage as an immediate response to injury, with increased sleep need, reduced total sleep time and highly fragmented sleep Duclos et al 2016, 2014, Wiseman-Hakes et al 2016, Wiseman-Hakes et al 2017 in press
- » For acute moderate-severe TBI, consolidation of the sleep-wake cycle was associated with recovery and clearing of PTA Wiseman-Hakes et al 2016
- » Those whose sleep-wake cycles were not consolidated and had the poorest sleep quality remained in PTA at time of discharge from ICU Duclos et al 2014, Wiseman-Hakes et al 2016

Evolution of Sleep Disorders: Moderate-Severe TBI- Acute



- » Alterations in sleep occur within first 24 hours following injury with immediate increase in sleep need
- » Characterized by increased day-time naps
- » Usually associated with fragmented night time sleep, poorer sleep quality
- » Associated with pain, mood

Wiseman-Hakes et al 2015 (unpublished), Wiseman-Hakes et al 2017 (in press)

- » May be neuroprotective as brain undergoes metabolic cascade and glucose need is increased
Glial cells are replenished during sleep

Evolution of Sleep Disorders: Concussion mTBI- Acute



- » During the chronic stage, disturbed sleep can be a manifestation of injury/damage to the brain AND... OR
- » Can also be secondary to pain, mood, alterations in activity level, weight gain, environmental changes to the circadian cycle due to lack of formal schedule
- » Can also be due to medication effects, neuroendocrine disruption, mood disturbances

Evolution of Sleep Disorders:
Moderate-Severe TBI-Chronic



- » Sleep disturbance in those with PPCS is typically characterized by symptoms of insomnia
- » Pre-existing history of sleep disturbance is a risk factor for development of persistent symptoms
- » In this population, disturbed sleep is usually associated with other factors such as mood, pain or cervical spine issues... etiology is unclear

Evolution of Sleep Disorders: Concussion/mTBI and Persistent Symptoms



A 'Famous' Quote by Beatrice the Biologist!



Why Does This Matter? Introduction to Normal Sleep





Sleep is of the brain, for the
brain, and by the brain Hobson 2005
Sleep is the price we pay for
neuroplasticity Tononi 2014



- » Sleep onset occurs in 10-20 minutes
- » 4 stages per night - 1, 2, 3, Rapid Eye Movement REM
- » NREM(1,2,3)-REM cycles = about 90 min
- » Approximately 5 cycles per night
- » SWS pressure higher in 1st half of night
- » REM predominates last half of night
- » Most of the night (up to 60%) in Stage 2

Normal Sleep

- Characteristics



- » Sleep plays a critical role in brain homeostasis
- » Recently, a *biomolecular clearance system* using convective flow between the cerebrospinal fluid (CSF) and interstitial fluid (ISF) to *remove toxic metabolites in the brain* was described.
- » Clearance during sleep is 2X faster than during wakefulness.

Xie L. et.al. Science 2013

- » In humans, the glymphatic system has been identified to remove beta-amyloid proteins during sleep

Mendelsohn & Warick 2013, Liff 2014

Sleep and Brain Homeostasis: Glymphatic System



» Unfragmented:
(minimal number of
arousals & awakenings)



» All the stages and adequate number of
cycles (4-5/night)

» Relatively small percentage of stage 1
sleep

» Good percentage of slow wave sleep and
REM sleep

What makes a 'good' sleep? >

» ‘Sleep disruption tends an organism towards being like an automatic machine-like operator, a reflexive and instinct-driven automaton, a being with diminished cognitive and behavioral flexibility’

Richard Horner University of Toronto, Dept. of Medicine, Canada Research Chair, Sleep and Respiratory Neurobiology The Universal Pastime: Sleep and Rest Explained (2015)

What Happens When We Don't Sleep?





Sleep, Wakefulness and Traumatic Brain Injury

Implications for Clinical Practice



- » Release of HGH during slow wave recovery sleep stimulates cell reproduction and regeneration
- » Cortisol released during latter half of sleep, (as melatonin levels dip) facilitates body's adaptation to stress, suppression of inflammation, enhancement of wound healing, modulation of plasma glucose & increased production of red blood cells

Mullington JM. Endocrine function during sleep and sleep deprivation. In: Stickgold R, Walker MP, eds. *The Neuroscience of Sleep* Amsterdam; Boston: Elsevier Academic Press; 2009. p. 209-212.

Role of Sleep in Recovery from Injury



- » Animal studies show that sleep deprivation impairs recovery after nervous system insult
- » Chronic sleep loss results in neuronal death, particularly in pre-frontal cortex

Roman V et.al. Sleep restriction by forced activity reduces hippocampal cell proliferation *Brain Res. Dec 2005* (1065 (1-2)).

Maquet P, Smith C, Stickgold R. *Sleep and Brain Plasticity*. New York: Oxford University Press Inc; 2003.

Walker M. Sleep-dependent memory processing. In: Stickgold R, Walker M, editors. *The Neuroscience of Sleep* San Diego, CA: Academic Press, division of Elsevier Inc; 2009.

Sleep is necessary for learning, cerebral plasticity and generation of new neurons in the adult human brain



- » ‘In a rodent model of TBI, enhancement of slow wave sleep (delta frequency) markedly reduced diffuse axonal damage in the cortex and hippocampus, and improved memory impairment 2 weeks after trauma. These results suggest that enhancing slow-wave sleep acutely after trauma may have a beneficial disease-modifying effect in subjects with acute TBI’.

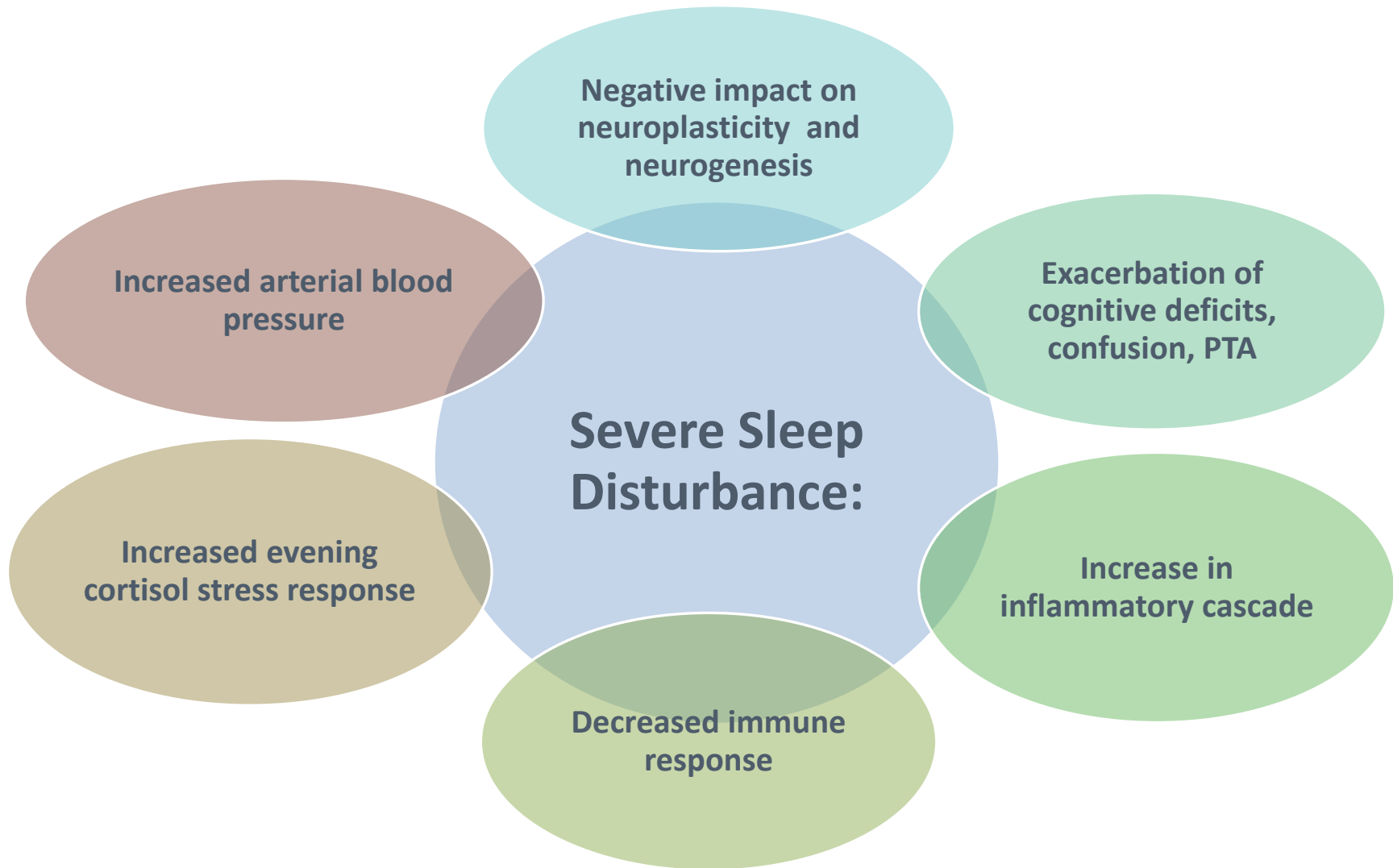
Morawska et al 2016. J Neuroscience

Role of Delta Sleep in Recovery



Acute Stage: Symptoms of Sleep Loss in ICU

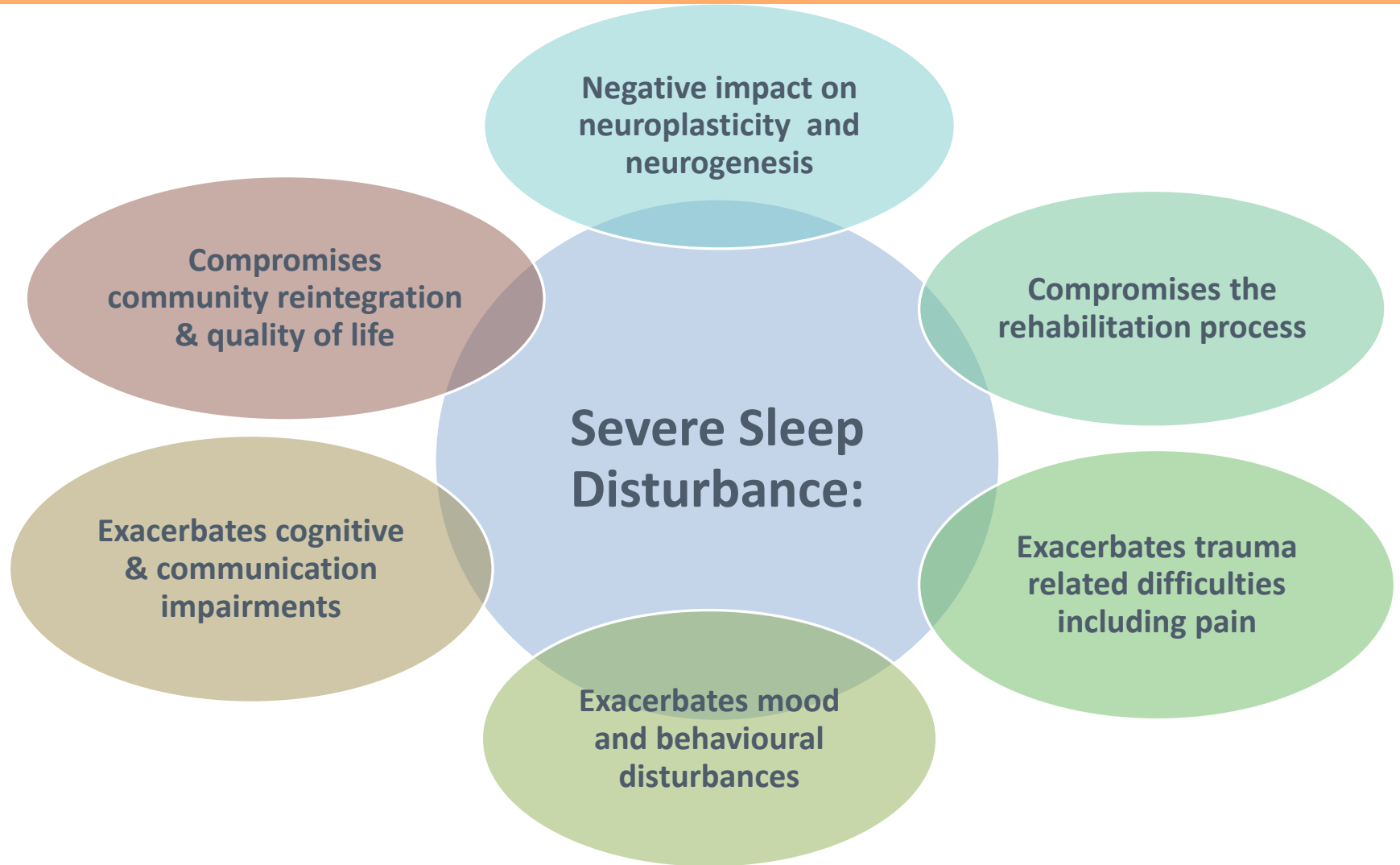
Duclos 2014 ©



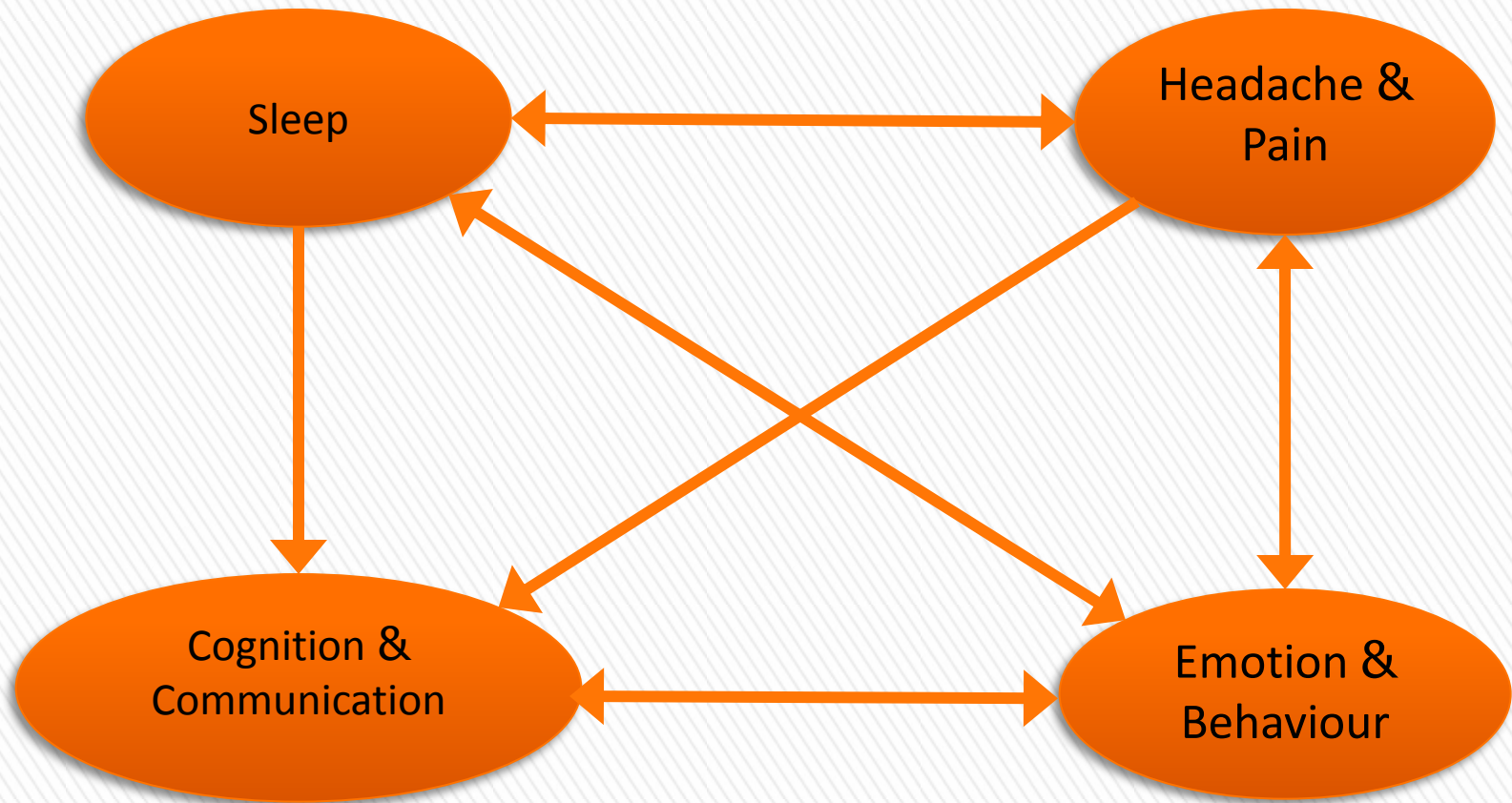
(Goel et al., 2009; Dinges et al., 1994; Shamsuzzaman et al., 2002; Spiegel et al., 2002; Ogawa et al., 2003; Ayas et al., 2003; Mullington et al., 2009; Spiegel et al., 1999; Lippert-Gruner, et al., 2007)

Chronic Stage: Sleep Disturbance and Recovery

Wiseman-Hakes 2014 ©



(Wiseman-Hakes et al 2016, 2014, 2013, 2011; Meerlo et al 2006)



Interaction of Symptoms & Sequelae >

- » Interventions to improve sleep and or wakefulness in a sample of adults with chronic TBI, 1-22 years post injury, resulted in significant and functionally relevant improvements in cognition; speed of information processing $p=0.007$, language/communication $p=0.01$ and depression 0.01

Wiseman-Hakes et al 2013

Impact of Treatment for Sleep on Outcomes



- » In the acute stage of concussion, mTBI , the brain is in a state of energy crisis, metabolic diaschesis
- » Brain requires glucose and energy for acute recovery, so the prevalence of delta waves may be an adaptive response to preserve energy for recovery
- » Presence of increased delta activity and reduced alpha activity as measured by waking EEG, may be useful as an objective biomarker of recovery

Sleep and Acute Concussion/mTBI



- » Sleep and Concussion Questionnaire-Revised (SCQ) Wiseman-Hakes & Oulette 2013
- » SCQ is the only self-report measure that quantifies changes in sleep in response to the brain injury and is useful in quantifying change in response to intervention or spontaneous recovery, and the scoring system can be used for triage purposes
- » Pittsburgh Sleep Quality Index
- » Sleep Diaries
- » Epworth Sleepiness Scale (Note: is NOT a measure of sleep)

Assessment: Self Report Measures



- » Actigraphy
- » Polysomnography
- » Multiple Sleep Onset Latency Test (MSLT)
- » Multiple Wake Test(MWT)
- » Urinary Melatonin (not a measure of sleep per se)

Assessment:

Objective Measures



Sleep

Interventions



- » Cognitive behavioural therapy (CBT) has been found to be efficacious Oullet & Morin 2004, 2007
- » One other case series did not find significant results, however participants (N= 3) did have secondary improvements in anxiety, depression, fatigue and pain Lu et al Neurorehabilitation 2016
- » If the insomnia is directly due to damage to the Ventral lateral pre-optic nucleus then CBT will not work Lu et al J of Neuroscience 2000

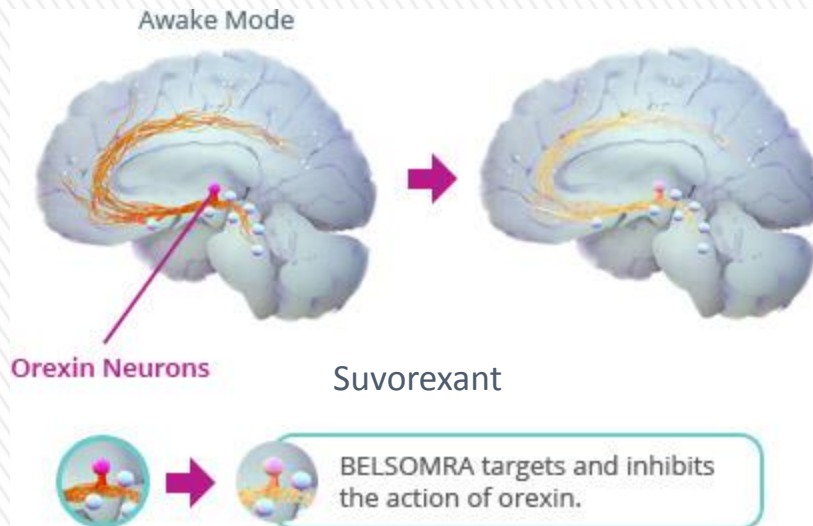
Insomnia & CBT



- » There are many neurotransmitters in the wake and sleep pathways that work together to promote wakefulness or sleep
- » Orexin is a key wake promoting neurotransmitter that sends signals to other wake promoting neurotransmitters to support their activity
- » Suvorexant is a relatively new pharmacological intervention for insomnia that is an orexin receptor antagonist i.e. selectively blocks orexin receptors

Pharmacological





<https://www.belsomra.com/how-belsomra-works/>

- Unlike other traditional pharmacotherapies for insomnia, it has no effect on GABA. Instead of promoting sleep, it inactivates wakefulness
- Adverse effects commonly observed with benzodiazepines and nonbenzodiazepines are not present
- Suvorexant can be used daily on a long-term basis with no risk of rebound insomnia or physical dependence Bennet et. al. Pharmacy & Therapeutics 2014
- Precautions exist for certain patient populations, including females, obese patients, and those with respiratory disease Norman et.al. Nature and Science of Sleep 2016

Mode of action

Preliminary evidence to indicate that acupuncture increases:

- » Evening melatonin production
- » Total sleep time
- » May be a secondary response to reductions in anxiety

Spence et.al. 2004, J Clinical Neuropsychiatry & Clinical Neuroscience:

- » Five weeks of acupuncture treatment (N=18 adults with anxiety and insomnia) associated with a significant ($p = 0.002$) nocturnal increase in endogenous melatonin secretion (as measured in urine) and significant improvements in polysomnographic measures of sleep onset latency ($p = 0.003$), decreased arousal index ($p = 0.001$), total sleep time ($p = 0.001$), and sleep efficiency ($p = 0.002$).

Acupuncture



- » Anecdotally reported as being efficacious in some cases
- » Mechanism is thought to be improvement (i.e. towards normalization) in tentorial length and angle in response to manipulation of the upper cervical spine
- » Recognition that a definitive recommendation cannot be made re efficacy due to low-level of current studies and heterogeneity of design; higher quality research is indicated

Hollenbach D. 2013 Can J Chiropractic Assoc.

Chiropractics



- » Ashwaganda is a herb known as “Indian ginseng,” that has been used Ayurvedic medicine for over 3000 years
- » Taken about 1 hour prior to sleep onset, it has been anecdotally reported to improve the ability to fall asleep (i.e. sleep onset latency)
- » Some research has shown it to be efficacious in controlling chemotherapy induced fatigue in cancer patients Biswal BM et.al. Integr Cancer Ther. 2012
- » Has also been found to reduce stress and anxiety in non TBI patients Chandrasekhar K, et.al. Indian J Psychol Med. 2012

Supplements



- » Magnesium and Zinc Rhondanelli et.al. 2011
- » Iron for those with low iron levels; considerable evidence that low iron/ferritin levels can cause periodic leg movement disorders Li et. al. 2015
- » Warm milk with a TBSP of Blackstrap Molasses prior to sleep onset (contains magnesium)

Supplements



Findings of a recent meta-analysis indicate that significant effects following Mindfulness Meditation Training were found in:

- » Reduction in total wake time,
- » Reduced sleep onset latency,
- » Increased sleep quality,
- » Increased sleep efficiency, and
- » PSQI global score; all $p < 0.05$)

Gong et. al. Meta-analysis J Psychosomatic Research 2016

Mindfulness Meditation



- » Sleep and wake disorders following TBI are pervasive and can compromise outcomes and quality of life
- » They need to be taken seriously with routine screening, formal evaluation where indicated.
- » There ARE treatments.....and sometimes treatment takes time to determine the best efficacy

Take Home

Message



» Questions?



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Thank-you!

