Sleep & Brain Injury

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Outline

1. The role of sleep in post-injury recovery
2. The effects of brain injury on sleep
3. Treatment: Improving sleep in the brain injured patient

Incidence

• TBI: 1.4 million/year in US
• Stroke: >795,000/year in US

Total: 2.2 million/year
Incidence of Sleep Disorders in Brain Injured Patients

TBI = 30 – 60 %

Stroke = 34 - 78%

690,300 – 1,460,000 NEW brain injured patients/year with sleep disorders

Collen 2011
Pasic 2011
Schuiling 2005

Sleep’s Role in Brain Function

• Memory consolidation
• Emotional Regulation
• Maintenance of neuronal functioning
• Critical to neurogenesis and neural plasticity

Consequences of Sleep Problems in Brain Injury

• Increased morbidity & mortality
• Increased neurocognitive deficits:
  - Impaired attention
  - Decreased information processing speed
  - Memory deficits
  - Impaired executive functioning
• Increased time in hospital & rehab

Castriotta 2011
Collen 2011
Consequences of Sleep Problems in Brain Injury

- Psychological problems – anxiety, depression, PTSD
- Increased pain
- Delayed return to work
- Adverse impact on social functioning

Sleep disorders increase functional deficits & undermine restorative processes

Fact or Fiction?

It's best not to let someone sleep immediately after a brain injury. If sleeping wake frequently to check on them.

Impact of Sleep Disturbance on Stroke Outcome – Animal Study 1

Design:
1. Sleep deprived for 6H during light phase 12H post surgery
2. Sleep deprived for 12H during light phase 12H post surgery
3. Sleep deprived during 12H light phase for 3 days post surgery (allowed to sleep in dark phase)
4. No sleep disturbance post surgery
5. Sham surgery controls w/ no sleep disturbance
Impact of Sleep Disturbance on Stroke Outcome – Animal Study 1

Results:
1. Sleep deprivation 1st 24 hours
   - 6H deprived = small ↑ infarct volume
   - 12H deprived = 40% ↑ infarct volume
   - 3 Days disrupted = 76% ↑ infarct volume

2. 12H deprivation = 137% damaged cells
   - 3 Days disrupted = 219% damaged cells

3. Add'l brain damage not reversible even when allowed to sleep for 24H after the 12H deprivation

P values range .001 - .017

Impact of Sleep Disturbance on Stroke Outcome – Animal Study 2

Design:
1. Ischemia with sleep disturbance
2. Ischemia without sleep disturbance
3. Sham with sleep disturbance
4. Sham without sleep disturbance

Deprivation of 80% sleep during normal 12H sleep period for 3 days post stroke
Impact of Sleep Disturbance on Stroke Outcome – Animal Study 2

**Results:** 5 weeks post-stroke:
- forearm motor skills, ↓axonal sprouting, ↓expression of synaptophysin, ↓synaptogenesis, ↓angiogenesis

**Conclusions:** Sleep plays a role in the recovery process. Promoting adequate sleep after stroke may be critical to improving neuroplasticity, brain restoration & functional outcomes.

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**Stroke & Rehabilitation**

**Design:**
- Groups = stroke vs no stroke, N = 36
- Sleep vs no sleep between practice & testing
- Continuous tracking task

**Results:**
- Stroke → significant learning only in group that slept

**Conclusions:**
- Sleep very important for motor skill learning & memory consolidation

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**Pathophysiology:**
What’s going on behind the scene?
Areas of Damage Impacting Sleep

Stroke
- brainstem
- thalamus
- thalamomesencephalic area
- pontine tegmentum

TBI
- diffuse axonal
- anterior hypothalamus extending into basal ganglia
- septum pellucidum
- corpus callosum
- deep gray matter
- dorso-lateral pons
- midbrain

Glymphatic System:
The Brain’s Cleaning System

- Corollary to lymphatic system
- Increased flow of CSF thru brain
- Clears toxins
- Works much more powerfully during sleep
Injury Related Biochemical Processes Impacting Sleep

- Inflammation
- Free radical formation
- Hyperglycolysis
- Hyperglycemia
- Neural excitotoxicity
  - ↓Hypocretin
  - ↓Nocturnal melatonin

Hypocretin

- Wake promoting neurotransmitter produced in hypothalamus
- Low CSF levels in 50% of TBI patients
- Levels often increase in 6 months
- Patients with continuing EDS have continuing low levels

Melatonin & Stroke

Comparison of ischemic stroke pts to healthy controls at 3 days & 2 weeks post-stroke

Results:
- ↓nocturnal urinary melatonin excretion:
  - 0.05 +/- 0.01 ng/ml vs 30 +/- 3.0 ng/ml (p=0.001)

May be associated with:
- 1) Changes in sleep pattern - ↑FNA, ↑naps, nighttime insomnia, daytime hypersomnia
- 2) Neuro & psych Sx (including mood disorders)
Addition Factors in Sleep
Problem Pathogenesis
- Psychological effects of the trauma
- Premorbid (injury) psychiatric problems
- Drugs
- Pain
- Psychosocial stressors
- Environmental factors

Fact or Fiction?
Many different sleep problems may occur following brain injury.

Sleep Architecture Changes
Type of change varies w/ site of damage

Types of Changes
- REM & NREM
- Delta activity
- ↓TST & SE
- Fragmentation
- Spindles, K complexes & vertex waves can be completely lost

Kryger 2011
Terzoudi 2009
Incidence of Sleep Disorders: General Population vs Brain Injured

Additional Sleep Disorders

- Parasomnias
  - Sleep walking
  - REM behavior disorder
  - Nightmare Disorder
- Sleep Related Movement Disorders
  - Periodic Limb Movement Disorder
  - Restless Legs Syndrome
- Narcolepsy
- Post Traumatic Hypersomnia

SCREEN ALL PATIENTS WITH TBI OR STROKE FOR SLEEP PROBLEMS
Fact or fiction?

Medication is the only effective way to treat sleep problems post brain injury.

Therapies

- Pharmacotherapy
- Cognitive & Behavioral Therapies
- Devices for Sleep Apnea
- Therapies for PAP Compliance
- Therapies for Circadian Rhythm Disorders

*Modifications may be necessary to accommodate for fatigue, diminished cognitive functioning, etc.*

Medication

**Hypnotics & Sedatives**

Benefits:
- Fast acting, may help short-term

Risks:
- ↑cognitive impairment, ↓memory, ↓new learning,
- compromise breathing, ↑daytime fatigue,
- interfere w/ neural plasticity & recovery,
- tolerance and/or dependence

Contraindicated:
- benzodiazepines, antihistamines, antipsychotics

Oulette 2007
Cullen 2011
Medication

**Melatonin**
- Insomnia
- Circadian Sleep Wake Disorders
- REM Behavior Disorder

Antioxidant
- Neuroprotective for oxidative stress after stroke?

Medication

**Activating agents**
- EDS & fatigue
  - Activating antidepressants
  - Atypical stimulants

Risk for pts with cortical stroke & some cardiovascular disorders

Cognitive Behavioral Therapy for Insomnia (CBT-I)

- Sleep Hygiene Education
- Cognitive Therapy
- Stimulus Control
- Relaxation Therapies
- Sleep Restriction/Compression
Meta-Analysis of CBT-I

- 23 RCT trials 1985 – 2014
- Varying comorbid medical & psychiatric disorders
- At least 4 face to face sessions, indiv or group

Results:
1. Large pre to post Tx effects on ISI & PSQI maintained thru 18 mos follow up
2. Little variation in outcome between comorbidities
3. Individual more effective than group

Study: CBT-I & TBI

- N = 11 TBI pts with post injury insomnia
- Single case design w multiple baselines
- 8 weeks CBT-I Tx
- Measures: Sleep diary, ISI, MFI, DBAS, BDI, BAI

Results:
↓ wake time in 73%, ↓ fatigue
↑ SE from 77.2% to 87.9%(post), 90.9%(3 months)
64% no longer met insomnia criteria
Even with cognitive deficits, pts able to engage in and benefit from CBT-I

CBT-I & TBI

[Graph showing Total Sleep Time and Sleep Efficiency improvements with statistical significance indicated.]

Oullett 2007
CBT-I & TBI

<table>
<thead>
<tr>
<th>Minutes</th>
<th>PRE</th>
<th>POST</th>
<th>MONTH</th>
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<tr>
<td>128</td>
<td>59</td>
<td>56</td>
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* Differences significant p<.017

Oullett 2007

CBT-I Effectiveness & Impact on Inflammation

- RCT N = 123
- Groups: CBT-I, Tai Chi, Sleep Seminar
- 4 month, 2H group/week Tx
- Outcome measures: sleep quality, insomnia Dx, C Reactive Protein level

**Results:**
- CBT-I group → much higher rate of remission of insomnia & only condition w/ improvements retained @ 1yr; significant decrease in CRP

Irwin 2014

Insomnia Remittance: C-Reactive Protein

<table>
<thead>
<tr>
<th>CRP (mg/dl)</th>
<th>Month 4</th>
<th>Month 16</th>
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* p< 0.05

CBT-I, RCT Design

Irwin 2014
### Additional Psychological & Behavioral Treatment Strategies

- **Behavioral Activation** – break cycle of low activity & physical deconditioning which further reduces activity – exercise can reduce fatigue and improve sleep
- **Scheduled naps**
- **Address environmental disruptions** – pain may lead to hypersensitivity to stimuli such as noise and temperature
- **Imagery Rehearsal Therapy** for nightmares
- **Psychotherapy** for depression & anxiety

### Devices for Sleep Apnea

- **Positive Airway Pressure Devices** (CPAP, BiPAP, APAP)
- **Oral Appliances**
- **Implanted upper airway stimulation device**

### CPAP & Stroke

![Graph showing CPAP & Stroke](Martinez-Garcia 2003)

- **Group I**
  - Tolerated CPAP (n=25)
  - New Vascular Events: Group I = 6.7%
- **Group II**
  - Non-Tolerated CPAP (n=25)
  - New Vascular Events: Group II = 36%
Statistics on CPAP Use

• ~1 in 5 do not initiate CPAP therapy
• ~50% of those using CPAP do not use it for enough time to benefit
• 50% not using CPAP at the end of 1 year

Patterns of adherence are established in the first week of treatment

Therapies for PAP Compliance

• Desensitization
• Relaxation
• Cognitive Behavioral
• Motivational Enhancement

Therapies for Circadian Rhythm Disorders

• Bright Light Therapy
• Melatonin
• Chronotherapy
• Exposure to synchronizing agents
  - Light
  - Mealtimes
  - Activities
Dietary Therapy? Branched Chain Amino Acids
- Precursor to glutamate synthesis
- Glutamate is excitatory to hypocretin neurons
- BCCA supplementation increases “glutaminergic input to hypocretin neurons”
- Increases wakefulness

NEWS FLASH! New Cure for Insomnia
Hillary’s emails better than Ambien

PEARLS
- The healing & recovery of the injured brain is dependent on sleep. Inadequate sleep may result in more extensive brain damage, compromise recovery, & increase morbidity & mortality.
- Most brain injured patients will have at least one sleep disorder.
- HHS & the Defense & Veterans Brain Injury Center recommend using cognitive-behavioral therapies before medications for sleep disorders in patients with brain injuries.
- Medication may be helpful, but should be used very judiciously.
References

- Gao B et al. Sleep disruption aggravates focal cerebral ischemia in the rat. SLEEP 2010;33(7):879-887.

Quick Screening for Sleep Disorders

1. How are you sleeping?
2. Do you snore loudly or wake up gasping for air?
3. How long does it usually take to fall asleep?
4. How often and for how long are you up most nights after bedtime?
5. Do you feel refreshed in the morning?
6. Do you have difficulty functioning and/or staying awake during the day?
7. Do you engage in any unusual behaviors during sleep?
Sleep Apnea: STOP-BANG
3 or More Positive Answers

- Snoring
- Tiredness during daytime
- Observed apnea
- High blood pressure
- BMI > 35
- Age > 50
- Neck circumference > 40cm
- Male gender

When to Refer to a Specialist

- SDB or CRSWD suspected
- Insomnia or EDS symptoms that do not rapidly resolve
- No improvement with basic sleep hygiene information
- Significant mood disturbance present along with sleep problem
- PAP adjustment problems
- Presence of unusual sleep behaviors

Ten Tips for Better Sleep

According to the National Sleep Foundation, 30% of us have moderately frequent symptoms of insomnia. Sleep is an important and necessary part of life. Without it we can't survive. Research indicates that it plays an important role in the restoration of our energy, the functioning of our immune system, healing, memory and emotional stability. It also affects the regulation of hormones that control appetite and metabolism which can contribute to weight gain or difficulty losing weight.

With some easy changes you can maximize sleep enhancers and minimize sleep disrupters to create a lifestyle and habits conducive to good sleep.

1. Begin with a comfortable sleep environment. Your room should be dark, comfortably cool and quiet. Your bed should feel good to you. Use your bed only for sleep and sex. Other activities in bed such as watching TV or working on your computer can interfere with sleep.

2. Be active. A busy and active lifestyle helps prepare you for good sleep at night. Physical activity, mental stimulation and meaningful activities are sleep enhancers. Exercise is a wonderful sleep medicine. Just make sure that you finish at least 3 to 4 hours before bedtime.

3. Dim the lights. Melatonin is our body's natural hormone that signals our brain that it is time to sleep. Darkness turns melatonin production on and light turns it off. The light from devices like computers and phones can have the same effect or be accentuated by high contrast for light. Exposure must be reduced in the evening. Reduce light exposure after 7 pm.

4. Avoid or limit alcohol in the evening. While alcohol may initially relax you, there is a rebound effect which results in increased arousal as it wears off. In other words, alcohol can be poison to sleep.

5. Avoid caffeine, nicotine and other stimulants, particularly late in the day. Caffeine within eight hours of bedtime can interfere with sleep.
6. Allow an hour before bed to wind down. Most of us need some time to calm our minds and bodies. Enjoy some quiet time and relax. The day and its work are over. Read, watch a light show on TV (with the brightness diminished) or even better, practice a form of relaxation or meditation. There is no need to go to sleep, but put away any work from the day. Glance at the clock, but avoid spending time staring at it.

7. Keep a regular schedule. This means not only having a regular bedtime and wake time, but also having your regular daily routine, such as meals, and exercise, at about the same time each day. Your body will respond and you will fall asleep more easily.

8. Don’t panic. Not sleeping well on any given night is not so important, but being anxious about your sleep can create a pattern of insomnia. If after following these tips you are still experiencing difficulty falling asleep, staying asleep or your sleep is not refreshing, then it is time to consult a sleep specialist for further help. Additionally, you should be evaluated if you experience food burning in your throat, acid reflux, frequent burping, nausea after eating, difficulty swallowing or other symptoms. An examination is an excellent and easy way to survey your throat, esophagus and stomach, during sleep or after you dream. The American Academy of Sleep Medicine at aasmnet.org can help you locate a behavioral sleep specialist in your community.

Dr. Marcy Wasman is a Licensed Psychologist specializing in Behavioral Sleep Medicine. Her practice is located in Miami, Florida.