Why Study Extremophiles?

Extremophiles are living organisms that survive and thrive in the harshest physical and chemical environments. Their study informs what is necessary to live and survive in these conditions and informs understanding of other living organisms.

Goals

• Discuss mechanisms by which sleep disturbance negatively influences acute recovery and chronic outcome following TBI
• List advantages and disadvantages of common sleep measurement metrics used in TBI
• Discuss the relevance of identifying specific sleep disorders to promote use of evidenced-based treatment

Acknowledgements

• This work is supported by the:
  – Defense Health Agency's Defense and Veterans Brain Injury Center and Subcontractor, General Dynamics Information Technology
  – Patient Centered Outcomes Research Institute
  – PCORI – CER-1511-33005

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• Studies described were approved by the Institutional Review Boards at James A. Haley Veterans Hospital (PR00000094, PR00000095, Pro00027954), Tampa, FL.

Disclaimers/Disclosures

• Disclaimer:
  – Contents may not represent the views of the Department of Veterans Affairs or the United States Government

• Financial Disclosure:
  – I certify that no party having a direct interest in the results of the research supporting this article has or will confer a benefit on me or on any organization with which I am associated AND, if applicable, I certify that all financial and material support for this research (e.g., NIH or NHS grants) and work are clearly identified.
Outline

• Sleep and TBI
  – Mechanisms for sleep disturbance in acute and chronic stages
  – Review incidence of sleep disturbance in acute moderate to severe TBI
  – Highlight association of acute sleep abnormality with rehabilitation

• Sleep Disorder Classification and Measurement
  – Briefly review categories of sleep disorders and consequences when unrecognized and untreated.
  – Discuss sleep assessment instruments used in inpatient rehabilitation settings.
  – Discuss TBI Model System studies highlighting specific sleep disorders and novel methods for inpatient rehabilitation.

• Research
  – Discuss TBI Model System studies highlighting specific sleep disorders and novel methods for inpatient rehabilitation.
  – Discuss future areas of research to improve the evidence base for assessment and treatment of post-TBI sleep disorders to maximize acute recovery and manage TBI as a chronic health condition.

Sleep & Neuroplasticity (Mechanism)

- Animal and human studies have shown that impaired sleep alters neurotransmitters
- Glutamate receptors, neuronal activation and related signaling molecules, as well as cognition and behavior
- Restriction of sleep alters several endogenous brain repair mechanisms including
- Axonal sprouting, synaptogenesis, neurogenesis, angiogenesis

Sleep Disturbance Rating (DelRS-R98)

<table>
<thead>
<tr>
<th>Sleep Disturbance Rating</th>
<th>Sequence 1 (initial evaluation)</th>
<th>Sequence 2 (second evaluation)</th>
<th>Sequence 3 (third evaluation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSI</td>
<td>24 days</td>
<td>29 days</td>
<td>33 days</td>
</tr>
<tr>
<td>No Sleep Dist.</td>
<td>25 (14.5%)</td>
<td>40 (23%)</td>
<td>65 (38%)</td>
</tr>
<tr>
<td>Mild</td>
<td>37 (21.5%)</td>
<td>52 (30%)</td>
<td>63 (30%)</td>
</tr>
<tr>
<td>Moderate</td>
<td>84 (49%)</td>
<td>73 (42%)</td>
<td>46 (27%)</td>
</tr>
<tr>
<td>Severe</td>
<td>26 (15%)</td>
<td>7 (4%)</td>
<td>10 (6%)</td>
</tr>
</tbody>
</table>


Sleep & Acute TBI

- Prevalence varies across studies (20-100%)
- Due to:
  - Measurement Methods
    - Self-report
    - Clinician Rating
    - Actigraphy
    - Polysomnography
  - Type of Sleep Disturbance
  - Time Since Injury
  - Patient Ability to Report

Examples of Mod-Severe SWCD using Objective Indices/ACG Confirmed Gross Data Collection

Table 1: Summary of studies examining sleep during inpatient TBI rehabilitation. Bolded studies represent worst of fit.

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>SWCD</th>
<th>2013</th>
<th>2016</th>
<th>2020</th>
<th>2021</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naka-Richardson et al., 2012</td>
<td>205</td>
<td>84%</td>
<td>74%</td>
<td>87%</td>
<td>88%</td>
<td></td>
</tr>
<tr>
<td>Zilman et al., 2012</td>
<td>205</td>
<td>78%</td>
<td>67%</td>
<td>78%</td>
<td>82%</td>
<td></td>
</tr>
<tr>
<td>Malley et al., 2009</td>
<td>14</td>
<td>78%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malley et al., 2008</td>
<td>31</td>
<td>68%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nakase-Richardson et al., 2008</td>
<td>127</td>
<td>68%</td>
<td>78%</td>
<td>78%</td>
<td>82%</td>
<td></td>
</tr>
<tr>
<td>Evans, Nakase-Richardson, et al., 2008</td>
<td>201</td>
<td>77%</td>
<td>78%</td>
<td>78%</td>
<td>82%</td>
<td></td>
</tr>
<tr>
<td>Nakase-Thompson et al., 2008</td>
<td>85</td>
<td>75%</td>
<td>75%</td>
<td>80%</td>
<td>82%</td>
<td></td>
</tr>
<tr>
<td>Burke et al., 2004</td>
<td>18</td>
<td>100%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Woehrle et al., 2012</td>
<td>28</td>
<td>76%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cohen et al., 1992</td>
<td>22</td>
<td>73%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: APM rise time; SWCD=Sleep-Wake Cycle Disturbance Reported in Study.
Sleep efficiency improved with PTA resolution.

Sleep improvement preceded resolution of other confusion symptoms.

Earlier improvement associated with earlier PTA and clearance and lower disability.

Improved characterization of sleep to facilitate appropriate sleep treatments.

Is sleep a treatment target?

-- Improved but
  - 63% remained with disturbance by Exam 3
  - 33% - moderate to severe

Sleep made unique contributions to
  - PTA and LOS

Is sleep a treatment target?
  - Improved characterization of sleep to facilitate appropriate sleep treatments

Type III Multiple Regression Results Demonstrating Additional Predictive Value of SWCD on Duration of PTA and LOS.

Model:

- LOS
  - Age
  - ED GCS
  - DPI
  - SWCD

- Model: PTA
  - Age
  - ED GCS
  - DPI
  - SWCD

Additional Predictive Value of SWCD on Duration of PTA and LOS.

Partial Model

Type III Multiple Regression Results Demonstrating Additional Predictive Value of SWCD on Duration of PTA and LOS.

Summary & Conclusions

- Improved but
  - 63% remained with disturbance by Exam 3
  - 33% - moderate to severe

- Sleep made unique contributions to
  - PTA and LOS

- Is sleep a treatment target?
  - Improved characterization of sleep to facilitate appropriate sleep treatments

A

When sleep disruption improves, other phenomenology (cognition, disorientation, agitation, fluctuation, psychotic symptoms) improve.

TBIMS studies have found that early phenomenology (including sleep-modifiable symptom) is related to outcome.
Outline

- Acute Sleep and TBI
  - Review incidence of sleep disturbances in acute TBI
  - Highlight association of acute sleep abnormality with rehabilitation outcome
  - Present role of sleep abnormalities on mechanisms of neural repair

- Sleep Disorder Classification and Measurement
  - Briefly review categories of sleep disorders and consequences when unrecognized and untreated
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- Research
  - Discuss TBI Model System studies highlighting specific sleep disorders and novel methods for inpatient rehabilitation
  - Discuss future areas of research to improve the evidence base for assessment and treatment of post-TBI sleep disorders to maximize acute recovery and manage TBI as a chronic health condition.

Purported Purposes of Sleep

- Restoration of Biochemical / Cellular substrate
  - Depleted substrate are replenished during sleep
  - SWS is associated with the release of Growth Hormone promoting protein, synthesis, anabolism, and cell repair
  - Potential Immune System Enhancement

- Restoration of Synaptic integrity and Responsiveness
  - Restoration of neurotransmitters (synapse of depleted aminergic and cholinergic substrate)
  - Restoration of synaptic integrity (synaptic transmission)

- Sleep Facilitates the Process of Memory / Learning
  - Information storage, organization and coordination for future recall, and integration with other stored data

Sleep is regulated by two body systems:

- Circadian Clock
  - Regulates timing of sleep and wakefulness, affected by environmental cues (light, sleep deprivation, physical stimulation etc)
  - SWS → Specific ordered replay of day's events (Hippocampus → Cortex)
  - REM → Hyperscanning (short term memory) → Cortex (long term memory)
  - This potentially facilitates the capacity for recall, and thus for later use

- Homeostatic Effect
  - The longer you are awake, the greater the need to sleep (Accumulation of Adenosine)

Sleep is regulated by two body systems:

Circadian Biological Clock

- Process C is Influenced by:
  - Light /Dark (Day / Night, Extraneous light)
  - Core Body Temperature
  - Cerebral Stimulation / Lack Thereof
  - Motor Activity / Quiescence
  - Feeding (Schedule/Hunger/Satiety)
  - Illness (fever, malaise, nausea, pain)
  - Medication/Drugs:
    - Intrinsic: Melatonin, Cortisol
    - External: Stimulants, Sedatives

Is there an optimal duration of sleep?
Primary Sleep Disorders
- Insomnia
- SRBD
- Hypersomnia
- CRSD
- Sleep Apnea

Environment/Circadian Misalignment
- Shift Work
- Light
- Noise
- Stress
- Blindness

Pharmacologic
- Prescribed
- Non-prescribed

Psychiatric
- Mental Disorders
- Psychological Distress

Medical Disorders
- Pain
- GERD
- Asthma
- Allergic Rhinitis
- Renal, Liver Failure
- Cardiac Ischemia

5-Finger Model to Sleep Management

Consequences of Disturbed Sleep
Disrupted Sleep Continuity
Inadequate Sleep
- Circadian Disruption
- Insomnia
- Sleep apnea

Adrenergic Response to Airway Obstruction
Obstructive sleep apnea

Nocturnal Hypoxemia
Central and Obstructive sleep apnea

Daytime Sleepiness / Fatigue
- Increased Incidence
- MVA / Workplace Accidents
- Impaired Cognitive Function
- Depression
- Irritability

Hypertension
Diabetes
Cardiac Dysrhythmias (Atrial Fibrillation)

Heart Attacks
Strokes

Outline
- Acute Sleep and TBI
  - Review evidence of sleep disturbance in acute TBI
  - Highlight association of acute sleep abnormality with rehabilitation outcomes
  - Presentation of sleep abnormalities as mechanisms of neural repair
- Sleep Disorder Classification and Measurement
  - Briefly review categories of sleep disorders and consequences when unrecognized and untreated
  - Review sleep assessment instruments used in inpatient rehabilitation settings
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- Research
  - Discuss future areas of research to improve the evidence base for assessment and treatment of sleep disorders following TBI and manage TBI as a chronic health condition

Sleep Assessments Used in Acute Rehabilitation
- Nursing Log
  - Sleep Graph (hourly “check-in” of open/closed)
- Self-report (patient/family asked)
- Actigraphy
- Polysomnography
  - Portable Bedside Device (Levels 2-4)
  - Sleep Laboratory (Level 1)

Actigraphy – Indirect Measure of Sleep
- Objective
- Accelerometer
- Many Models on the Market Today
  - Good/fair
  - Limb, Waist, Head Attachments
  - Used for Extended Interval
  - Statistics Provided
- Sleep, Wake, Light Exposure
  - Total sleep time
  - Sleep efficiency
  - Activity (Mean or Sum per epoch)
  - Light exposure
  - Duration of light exposure
Concordance of Actigraphy With Polysomnography in Traumatic Brain Injury Neurorehabilitation Admissions

**Objective Actigraphy Can Help Identify Specific Disorders to Inform Treatment – e.g. Circadian Rhythm Disorder (Irregular Type Displayed)**

- Blue = sleep interval
- Yellow = white light
- Black = movement

**Results: Consistency**

<table>
<thead>
<tr>
<th></th>
<th>All 3 days of monitoring ≥80% (NORMAL)</th>
<th>Not all 3 days of monitoring ≥80% (ABNORMA)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample size</td>
<td>48 (60%)</td>
<td>62 (82%)</td>
<td>.950</td>
</tr>
<tr>
<td>Time since injury to ACG</td>
<td>34, 52, 129</td>
<td>35, 60, 149</td>
<td>.298</td>
</tr>
<tr>
<td>GCS</td>
<td>3, 7, 13</td>
<td>3, 8</td>
<td>.114</td>
</tr>
<tr>
<td>Time to follow commands</td>
<td>0, 10, 36</td>
<td>3, 18, 93</td>
<td>.008</td>
</tr>
<tr>
<td>Duration of PTA</td>
<td>6, 26, 105</td>
<td>30, 71, 298</td>
<td>.008</td>
</tr>
<tr>
<td>FIM cognitive score at admission</td>
<td>13, 21, 20</td>
<td>5, 14, 19</td>
<td>.027</td>
</tr>
<tr>
<td>FIM motor score at admission</td>
<td>21, 58, 73</td>
<td>13, 24, 53</td>
<td>.011</td>
</tr>
<tr>
<td>DRS score at admission</td>
<td>6, 7, 16</td>
<td>9, 13, 21</td>
<td>.037</td>
</tr>
</tbody>
</table>

**Measures / Procedure**

- Polysomnography with EEG (Sommedics Somnostar)
- Simultaneous Respironics Actiwatch 2 / Spectrum Actigraphy

- Indices Compared:
  - Total Sleep Time (TST) – the amount of sleep in minutes recorded by a definitive period.
  - Sleep Efficiency (SE) – a ratio of the proportion of sleep in a defined period divided by the duration of that period.

*For the Overall Sample:*

- Total Sleep Time, r = .78, p < .01 (PSG = 316 minutes vs ACG = 325 minutes)
  - For PSG = sleep is determined by EEG. For Actigraphy, sleep is determined by accelerometers.
- Sleep Efficiency, r = .66, p < .01 (PSG = 78% vs ACG = 77%)
  - Non-significant differences between PSG/ACG across OSA, severity, spasticity groups. ACG may serve as a valid tool indirectly measuring sleep in TBI.
  - However, those with spasticity on the limb used to monitor sleep may require further study.

**For Eligible, Consecutive**

- 86% capture rate
- ACG loss due to:
  - Abbreviated LOS
  - Computer issue/data loss
  - Staff availability

Nakase Richardson R, Modarres M, Fogelberg D, Travis - Seidl J. Measurement of sleep in neurorehabilitation: The role of actigraphy. Symposia presented at the American Congress of Rehabilitation Medicine Conference; October 2017; Atlanta, GA.
Minimum of Seven
Little guidance exists to inform clinicians’ approach to OSA.

Assessment for specific sleep disorders is critical to the delivery of evidence-based care.

First study to use advanced diagnostics during inpatient rehabilitation to formally diagnose sleep apnea in consecutive admissions (N=86, unbiased sample)

1 in 2 of admissions were diagnosed with primarily obstructive sleep apnea

Traditional risk factors were not predictive of sleep apnea status except age (median age 37) and hypertension

Sleep Recording Equipment has been categorized into 4 levels by AASM

Sleep Recording Equipment has been categorized into 4 levels by AASM

Categories of PSG Sleep Monitoring Equipment

Two Consequences of OSA
The frequent disruption of sleep
The low oxygen level while asleep

Cause or exacerbate:
- Hypertension (high blood pressure)
- Hyperglycemia (Elevated Blood Sugars) making control of Diabetes more difficult
- Heart problems: Atrial Fibrillation, Worsening Congestive Heart Failure, Heart Attacks
- Strokes
- Headaches (particularly awakening with a headache)
- GERD (Gastric Acid Reflux)
- Impotence / Sexual Dysfunction (males and females)
- Depression
- Sleepiness / Fatigue during the day
- Increasing the risk of accidents (driving accidents and others)
- Cognitive Dysfunction (inability to focus on task and learn new things)
- Inattentiveness

Economic Impact of Sleep Apnea

- **12.4 billion** (in 2015) – Cost of diagnosing and treating OSA (U.S.)
- **$149.6 billion** (in 2015) – Cost of undiagnosed OSA
- **$49.5 billion** (in 2015) – Cost of diagnosing and treating every American adult who has OSA
- **$100.1 billion** (in 2015) – Projected savings in a single year in the U.S.


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  - Discuss TBI Model system studies highlighting specific sleep disorders and novel methods for inpatient rehabilitation
- Research
  - Outline future areas of research to improve the evidence base for assessment and treatment of TBI-related sleep disorders to maximize acute recovery and manage TBI as a chronic health condition
- Cost of diagnosing and treating every American adult who has OSA

Next Steps

- The Clinical Dilemma
  - Assessment for specific sleep disorders is critical to the delivery of evidence-based care.
  - Poor characterisation of the sleep disturbance can lead to delivery of the wrong treatment.
  - Little guidance exists to inform diagnosis (TBI physicians, sleep medicine) approach to assessment of specific sleep disorders such as sleep apnea in the acute rehabilitation setting for moderate to severe TBI patients.
- Stakeholder Input
  - Clinicians/Scientists
    - GBC Think Tank Meeting-Prioritized earlier diagnosis of OSA
  - Patients/Families (focus groups/surveys)
    - “[TBI] can’t imagine a problem more important than helping TBI persons regain the ability to regulate their normal sleep patterns”
  - Non-TBI Stakeholder Input (Agency for Healthcare Research and Quality)
    - Future Research Needs Papers 116,112 - Sleep Apnea Diagnosis & Treatment
Comparison of Sleep Apnea Assessment Strategies to Maximize TBI Rehabilitation Participation and Outcome (C-SAS)

PI: Risa Nakase-Richardson, Ph.D., FACRM

- Patient Centered Outcomes Research Institute (PCORI)
  - C-SAS Award July, 2017 for $2.68 million to TVREF/James A. Haley Veterans Hospital
  - 8 subcontracts with collaborating centers
  - Clinical Trials Identifier: NCT03033901
  - Using VA, DOD, and HHS funded TBI Model system infrastructure

Investigators

- James A. Haley Veterans Hospital, Tampa (lead)
  - Dan Schwartz, M.D. (and USF)
  - Carol Kalero, M.D. (and USF)
- Moss Rehabilitation Research Institute, Philadelphia
  - John Whyte, M.D., Ph.D.
  - Tom Watanabe, M.D.
- Ohio State University, Columbus
  - Jennifer Bogner, Ph.D., ABPP
  - Ulysses Magalang, M.D.
- Baylor Rehabilitation and U.T. Southwestern, Dallas
  - Kathleen Bell, M.D.
  - Marie DahDah, Ph.D.
- U. Washington, Seattle
  - Jeanne Hoffman, Ph.D.
- Craig Hospital, Denver
  - Cindy Harrison-Felix, Ph.D.
  - Kim Monden-Ph.D.
  - Dave Mellick, M.S.
  - Jessica Ketchum, Ph.D.

Stakeholders

- Policymakers & Administrators
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  - Colonel Geoffrey Grammer, M.D.
  - Colonel Sidney Hinds, M.D.
  - Linda Picon, MCD, CCC-SLP
  - Steve Scott, D.O.
  - Jill Massengale, ARNP, DNP
- clinicians
  - Kathryn Keiffer, SLP
  - Christina Monemayor-Wong, RN
  - Kerri Martin, OTR/L & Amy Pieragostini, OTR/L
- Industry
  - Mark Aloia, Ph.D.
  - Phillips
  - Carefusion
  - Nox-T3 Medical

Procedure

- All TBI Model System Participants consenting to C-SAS will be screened for determining PSG eligibility.
  - TBIMS National Data Central is centralized data management center.
- Certified sleep technologists (RSPGT) administered all tests
- Centralized Sleep Scoring and Interpretation Center
  - Blinded centralized RSPGT scoring and interpretation by board-certified sleep medicine physician(s) in Tampa.
- Outcome measures collected clinically or by trained research staff following TBI Model System procedures.

Aim 1: Compare Screening Tools to the “Gold Standard” for Determining Risk of OSA

<table>
<thead>
<tr>
<th>Paper-Pencil Screening Questionnaires</th>
<th>Actigraphy Watches Activity-Based Sleep Estimations</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=259</td>
<td>Level 1 Polysomnography Lab-Based, Criterion Study</td>
</tr>
</tbody>
</table>

Aim 2: Non-inferiority of Portable PSG (Level 3) to Attended EEG-PSG (Level 1) in Determining Sleep Apnea in TBI Patients During Inpatient Rehabilitation

<table>
<thead>
<tr>
<th>Level 1 Polysomnography Lab-Based, Criterion Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=259 Both Simultaneously</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Level 3 Polysomnography Portable, Home or Hospital Bedside Testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=259</td>
</tr>
</tbody>
</table>

N=81 Consented
N=70 Eligible
N=49 Completed
N=7 Pending PSG

Diagnostic Rates (Level 1)

- 71% Rate of Sleep Apnea
  - 67% Obstructive (Airway Blocked)
  - 2% Central (Failure to Initiate Breathing)
  - 2% Mixed (both)
- Discrepancy Between AASM Criteria for Sleep Apnea and Medicare Definition (degree of desaturation differs – 3% vs 4%.

Challenges

- Sleep Technician Availability
  - Implementation Challenge?
- Discharge Before PSG Completed
- Equipment Challenges
  - Staff Familiarity
  - Failure and Damage by Patients
- Last Minute Refusals / Agitation

Impact

- First study to identify screening and diagnostic methods for OSA in the TBI inpatient rehabilitation setting.
  - Improved access to OSA diagnosis and treatment
- Early identification of sleep apnea may improve TBI outcomes through traditional treatments (C-PAP, MAD).
  - Future work to compare treatments given low compliance rates

Thank you!

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Thank you!

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