Photosensitivity and Pain in Traumatic Brain Injury

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mTBI Symposium
12/13/2019
TBI and Chronic Pain

- Chronic pain is a common complaint from individuals with TBI (Nampiaparampil, 2008)
- Can occur in individuals 10+ years out from initially head injury

![Graph showing Pain Complaints and TBI Severity vs Pain](adapted_from_Balba_Elliot_et_al._2018)

*Adapted from Balba & Elliott et al., 2018*
Central Sensitization

- Chronic pain often explained by “central sensitization”: heightened activity in pain-processing circuits at the spinal cord and in brain
- Responsible for allodynia and hyperalgesia
- Direct demonstration of central sensitization difficult in patients
A Link between Light and Pain

- In rodent models, light can activate nociceptive neurons while simultaneously inhibiting anti-nociceptive neurons.

- Patients with fibromyalgia report higher levels of photosensitivity, light can activate pain-related circuitry in these subjects.

Martenson et al., 2016

Harte et al., 2016
Photosensitivity and Pain in TBI

- Photosensitivity is a common symptom after TBI and can last for years after injury (Callahan et al., 2016; Balba et al., 2018)

- Photosensitivity complaints are correlated with pain complaints

Adapted from Balba & Elliott et al., 2018
Rationale for Current Study

1. Test photosensitivity and pain thresholds using more objective measures in TBI subjects, with and without symptoms, and non-TBI subjects

2. Determine whether photosensitivity is related to clinical pain complaints and whether light can activate pain-related circuitry in TBI subjects suffering from chronic pain
Methods

• Quantify visual photosensitivity thresholds (VPT) using Ocular Photosensitivity Analyzer

• Provides a continuous variable of photosensitivity using objective stimuli
Methods

- Quantify pressure pain thresholds and tolerance levels using pressure algometry
- Correlates with pain complaints in other chronic pain populations
- Has been gold standard in pain research
Differences in Self-Reported Chronic Pain

Chronic Pain Impact Score

<table>
<thead>
<tr>
<th>No TBI (N = 113)</th>
<th>asymptomatic TBI (N = 107)</th>
<th>symptomatic TBI (N = 135)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SIQR Score</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No-TBI</td>
<td>aTBI</td>
<td>sTBI</td>
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</tbody>
</table>
| ![Graph](chart1.png)

Degree of Widespread Pain

<table>
<thead>
<tr>
<th>No-TBI</th>
<th>aTBI</th>
<th>sTBI</th>
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</table>
| ![Graph](chart2.png)
No Differences in Pressure Algometry

Pressure Threshold Levels

Pressure Tolerance Levels

No TBI (N = 113)
asymptomatic TBI (N = 107)
symptomatic TBI (N = 135)
Strong Correlation between VPT and Chronic Pain

VPT Levels

- No TBI (N = 113)
- Asymptomatic TBI (N = 107)
- Symptomatic TBI (N = 135)

VPT vs Chronic Pain Scores

- All subjects: $r = -0.51; p < 0.001$
- No TBI: $r = -0.40; p < 0.001$
- Asymptomatic TBI: $r = -0.34; p = 0.001$
- Symptomatic TBI: $r = -0.36; p < 0.001$
A Marker in Chronically Symptomatic TBI

- Symptomatic TBI group exhibit higher levels of chronic pain, sleep disturbances, depression, PTSD symptoms, and disability than asymptomatic and non-TBI groups.
Conclusions

• Photosensitivity could be used as a marker of central sensitization in “high-impact” chronic pain populations
  • These populations are often treated with ineffective opioid medications, this novel marker could inform new treatment options

• Future Directions:
  • Currently collecting fMRI data to test whether light is activating pain-related circuitry in out symptomatic TBI population
  • Longitudinal studies that track the progression of photosensitivity following TBI
  • Continuing rodent studies to better understand neural circuitry
Acknowledgments

Portland VA/OHSU:
Mary Heinricher, PhD
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:
Matt Butler, PhD
Scott Mist, PhD
Kim Jones, PhD
Binyam Nardos, PhD
Megan Callahan, PsyD

Current support:
NIH TL1TR002371 (NMB)
DoD PH-TBI Award W81XWH-17-1-0423 (MMH &MML)
RRD SPIRE and Merit Award (MML)
NIH BUILD EXITO Institutional Core
Portland VA Research Foundation
OHSU Medical Research Foundation
Links Between Light and Pain

- The rostral ventromedial medulla (RVM) is a key brain region encoding painful stimuli.
- Electrophysiological recordings have characterized 3 types of neurons, 2 of which are responsive to painful stimuli:
  - ON-cells
  - OFF-cells
Links Between Light and Pain

- Response linked to intrinsic photosensitive retinal ganglion cells (ipRGCs)
- Encode environmental light levels through their activity
- Part of non-image forming vision
- Project to the olivary pretectal nucleus (OPt)
  - When OPt is blocked, ON/OFF cells no longer respond to light
“Triple (+) diagnosis” group reports more symptomatic TBI than all other groups ($P < 0.001$)
ROC by Evaluation Congruency

- Number of positive diagnoses has a significant effect on accuracy of model:
  - Triple (+) had significantly higher AUC than Single (+) or Double (+).
  - Single (+) and Double (+) were no better than chance!

- TBI status is predicted by NSI scores only in Triple (+) subjects.

AUC=0.59; 95% CI [0.40, 0.61]; P = 0.01
AUC=0.51; 95% CI [0.49, 0.61]; P < 0.001
AUC=0.76; 95% CI [0.68, 0.84]
(Moulton, 2009)
Nociceptive inputs

Effectors:
- Changes in the threshold and activation kinetics of NMDAR and AMPAR
- Changes in the trafficking of AMPA receptors into the membrane
- Alterations in ion channels to increase inward currents & reduce outward currents
- Reductions in the release or activity of GABA and glycine

Cellular processes:
- Increase of membrane excitability
- Synaptic facilitation
- Disinhibition

Central sensitization:
- Development of or increases in spontaneous activity
- Reduction in threshold for activation by peripheral stimuli
- Enlargement of their receptive fields (conversion of nociceptive-specific neurons to wide dynamic neurons that now respond to both innocuous and noxious stimuli)
VPT vs Threshold

R = 0.21572  Intercept = 1.5955  Slope = 0.0013843  P = 0.00022566
VPT vs Tolerance

\[ R = 0.29304 \quad \text{Intercept} = 1.2245 \quad \text{Slope} = 0.0014619 \quad P = 0.00000045297 \]
Tolerance vs SIQR

\[ R = 0.18355 \quad \text{Intercept} = 628.05 \quad \text{Slope} = -1.5876 \quad P = 0.0014075 \]
Threshold vs SIQR

R = 0.086904  Intercept = 358.95  Slope = -0.56795  P = 0.13186
VPT vs SIQR

R = 0.50568  Intercept = 2.7094  Slope = -0.021467  P = 0.0000000000000001