Vision Rehabilitation

Treatment, Mitigation, and Recovery of Visual Function in Blast-related Traumatic Brain Injury

Photophobia (e.g., abnormal light sensitivity, photalgia) symptoms include eye pain at light levels easily tolerated by others. In traumatic brain injury (TBI) populations, photophobia is commonly associated with headaches, difficulties in concentration, and diminished cognitive function. In fact, over 60 percent of Service members and Veterans with blast-related TBI suffer from excessive light sensitivity that can seriously interfere with their daily and professional lives, and may persist for years (*Capo-Aponte et al. 2012, Gentleman et al. 2004*). Researchers at the Smith-Kettlewell Eye Research Institute (San Francisco, California) conducted a study to investigate two proposed mechanisms of TBI-related photophobia:

1. That a primary mechanism of photophobia is disruption of retinal function at high light levels
2. That TBI-induced edema in the brainstem can be a causal mechanism of photophobia

Service members are susceptible to both blast and non-blast concussive injuries, which often result in intractable photophobia. The present results provide the basis for non-invasive biomarkers for both the retinal and the deep brain mechanism of such photophobia.

To assess the respective contributions of these mechanisms of photophobia in mild traumatic brain injury (mTBI), and to provide biomarkers for such mechanisms, the project involved a polymodal suite of five non- invasive methodologies: behavioral pain assessment (nociphysics), electroretinogram (ERG), high-density electroencephalogram, functional magnetic resonance imaging, and tensor-based morphometric magnetic resonance imaging. Analysis of the results in the past year has shown support for both hypothesized mechanisms of mTBI-related photophobia.

In relation to the retinal etiology hypothesis, the ERG measures across the wavelength spectrum showed a striking difference between the full-intensity ERGs for the non- photophobic TBI group, which were close to normal photopic ERGs, and those for the photophobic TBI group, in which the ERG revealed a dramatic switch from cone- to rod- mediated function (*Tyler and Likova 2017b, 2017a, Tyler and Likova 2017c*; Figure 1). This switch supports an unprecedented explanation: that the light-induced pain at high light levels originates from the unsuppressed firing of the 100 million rod photoreceptors in the retina. The discovery of a retinal mechanism for chronic photophobia, which affects about half of the millions of TBI sufferers, gives this condition a scientific and medical respectability to bring it out of the shadows of an untreatable symptomatic and apparently psychogenic condition to a quantifiable syndrome with a well-defined non-invasive biomarker. This explicit etiology can guide specific physiological and genetic-engineering-based therapeutic approaches to correcting the debilitating condition.

The second hypothesis, that brainstem edema measured by tensor-based morphometry could provide a biomarker for the role of the trigeminal system in mediating the light induced pain, was also successful (*Likova and Tyler 2017*). In the non-photophobic group, the predominant effect was a swelling at pontine/medulla junction, in the region of the vestibular nuclei. In the mild photophobia groups, on the other hand, there was shrinkage in the general location of the trigeminal complex (Figure 2).

The project was successful in supporting both hypotheses of the roles of separate parts of the extended visual pathway assessed by appropriate non-invasive methodologies, in the painful light sensitivity that persists in many cases of blast-related TBI.

This study was funded by Psychological Health/Traumatic Brain Injury Research Program, and is strategically aligned to Clinical and Rehabilitative Medicine Research Program. The award (W81XWH-14-1-0416) was managed by Congressionally Directed Medical Research Programs.

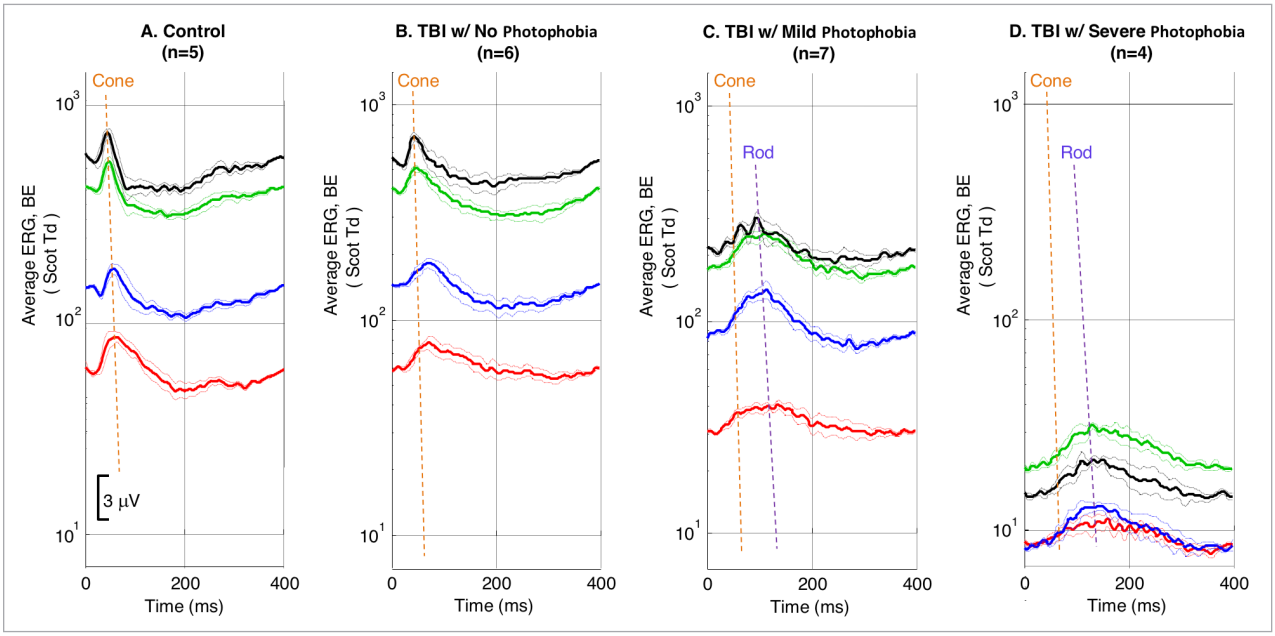

FIGURE 1: Group ERG analysis of the differential retinal responses in TBI and photophobia. Figure legend: Average ERG for control (A) and non (B), mild (C), and severe (D) photophobia groups for red, green, blue and white color fields (red, green, blue and black traces), scaled in terms of scotopic retinal illuminance. Dotted lines are ± 1 standard error of the mean ranges. The dashed red line tracks the location of the cone b-wave peak as a function of illuminance, while the dashed black line tracks time of the rod b-wave. Note that brain trauma without photophobia (Non-Ph mTBI) substantially alters the ERG waveforms at the highest intensities (B), losing the photophobic negative response following the positive peak (in A), but with little change in the peak times, whereas mild photophobia (mild-Ph mTBI) shows a marked slowing of the peak response (C), despite the illuminances remaining in a range overlapping with the controls. The severe photophobia (severe-Ph mTBI) group (D) shows further slowing attributable to the low illuminances, as the peaks align with the rod function predicted from the mild photophobia group. (Figure used with permission from the authors)

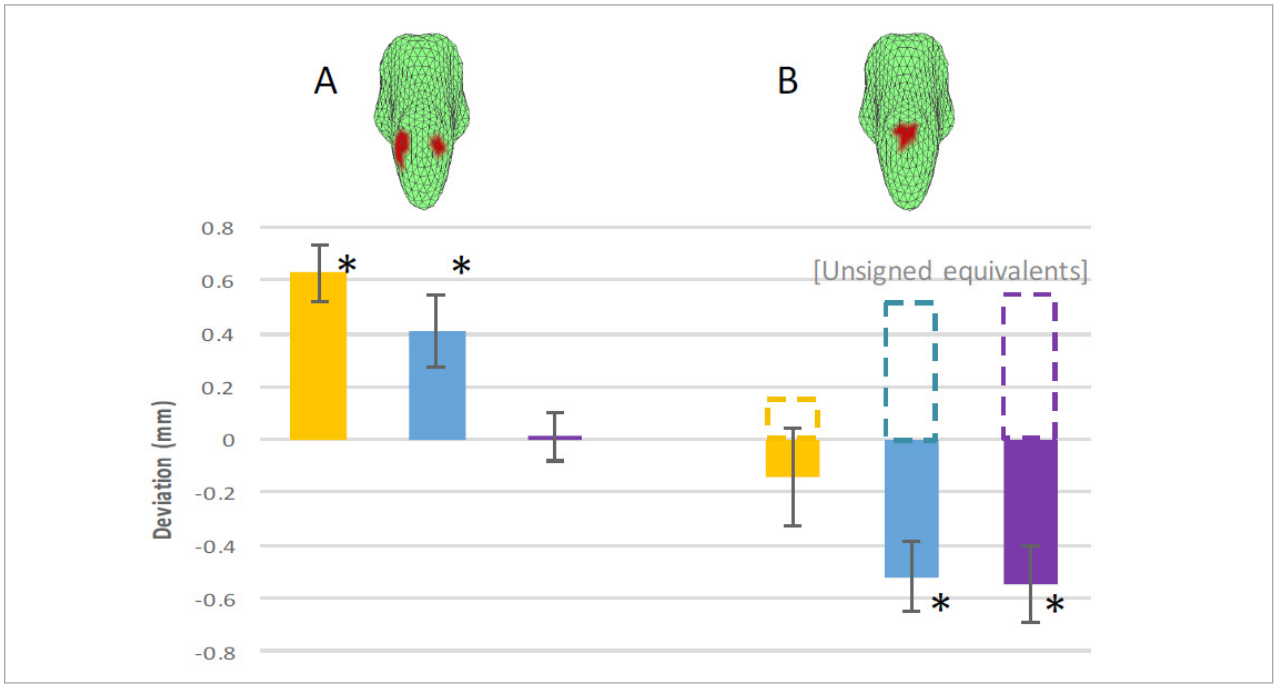

FIGURE 2: Quantitative TBM analysis of the human brainstem. Figure legend. Values of the average deviation for each of three mTBI groups for each of the two masked regions specified by the icons above the bar graphs. Non-Ph mTBI: yellow; mild- Ph mTBI: blue; severe-Ph mTBI: purple. Error bars represent one standard error of the means. Asterisks: significance at $p < 0.05$ after Benjamin/Hochberg correction for multiple tests at a false discovery rate of 0.05. (Figure used with permission from the authors)

REFERENCES:

Capo-Aponte, J. E., Urosevich, T. G., Temme, L. A., Tarbett, A. K., and Sanghera, N. K. 2012. "Visual Dysfunctions and Symptoms During the Subacute Stage of Blast-Induced Mild Traumatic Brain Injury." Mil Med 177 (7):804-13.

Gentleman, S. M., Leclercq, P. D., Moyes, L., Graham, D. I., Smith, C., Griffin, W. S., and Nicoll, J. A. 2004. "Long-Term Intracerebral Inflammatory Response after Traumatic Brain Injury." Forensic Sci Int 146 (2-3):97-104. doi: 10.1016/j.forsciint.2004.06.027.

Likova, L. T., and Tyler, C. W. 2017. "Traumatic Photalgia Changes in the Human Brainstem: Tensor-Based Morphometry." 47th Annual Meeting of the Society for Neuroscience, Washington, DC, November 11-15, 2017.

Tyler, C. W., and Likova, L. T. 2017. "How Traumatic Brain Injury Affects the Human Retina." Vision Sciences Society, St Petersburg, FL, May 19-24, 2017.

Tyler, C. W., and Likova, L. T. 2017. "How Traumatic Brain Injury Affects the Human Retina." F1000 Research 6 (6):981. doi: http://dx.doi.org/10.7490/f1000research.1114303.1.

Tyler, C. W., and Likova, L. T. 2017. "Studying the Retinal Source of Photophobia by Facial Electroretinography." Optom Vis Sci 94 (4):511-518. doi: 10.1097/OPX.0000000000001064.