TBI Biomarkers

Structural Alterations to Neurons Following Stretch Injury In Vitro

There is evidence that different regions of the brain exhibit different material properties, potentially leading to varying tolerances to traumatic injuries such as TBI. One theory to explain this difference is regional differences in the ratio of different brain cell types, specifically neurons/glia (Figure 1). The influence of mechanical loading on the brain was assessed by systematically injuring a mixed culture of primary neurons and glia in culture with known loading conditions, and quantifying measures to evaluate structural alterations.

The study revealed that altering the ratio of neurons to glia changes the response of neurons following stretch injury (Figure 2; *DiLeonardi et al., 2018a*). To understand the injury mechanisms responsible for functional deficits, a link between the mechanics of brain injury and the functional consequences must be provided. Current work utilizes a new state-of-the-art mechanical stretcher (MEASSuRE). The MEASSuRE system delivers a tailorable load to cultured neurons while simultaneously recording cellular electrical activity and high-speed imaging. MEASSuRE allows, for the first time, the evaluation of changes in neuronal activity from the (1) control, undamaged state, to the (2) initial primary injury, and (3) through the downstream secondary injury cascades in one continuous data stream, with temporal resolution. Preliminary data verifies a strain response measured directly from the neurons in culture during stretch injury (Figure 3; *DiLeonardi et al., 2018c*). Through this study, injury criteria can be established for use in classification of injury and to support computational models for the development and evaluation of future protective equipment.

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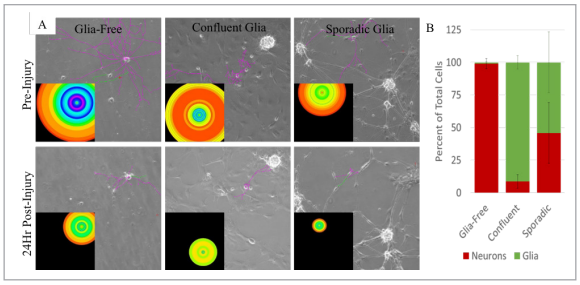

FIGURE 1: A) Pre- and Post-stretch images of cultures under different glia conditions. Neurites are traced to quantify number of branch points. Heat map rings show number of branch points as a function of distance from the cell body. B) Quantification of neuron to glia ratio based on different glia conditions. (Figure used with permission from the authors).

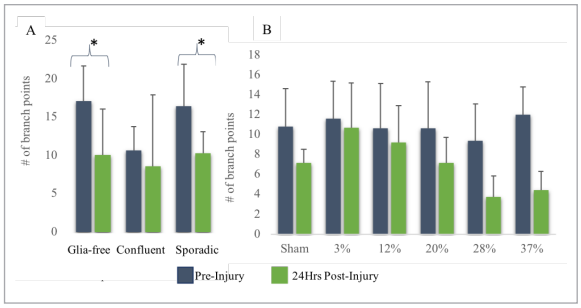

FIGURE 2: A) Quantification of neurite branching following stretch under different glia conditions. Significant decrease in amount of branching when no or sporadic glia present. No effect of injury on branching when glia form a complete uniform layer. B) Quantification of branching following different strains (3, 12, 20, 28, and 37 percent). Threshold for structural damage between 20 and 28 percent. (Figure used with permission from the authors).

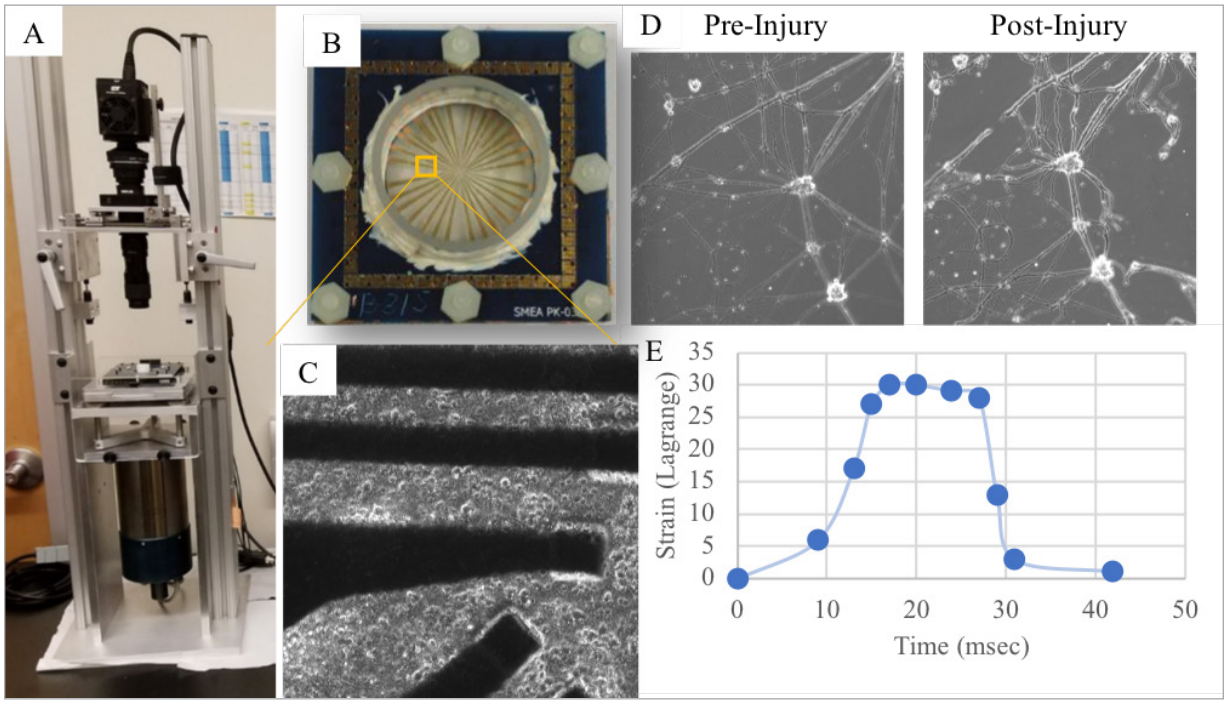

FIGURE 3: A) New MEASSuRE equipment. B) Example of a stretchable microelectrode array (sMEA). C) Example of neuronal culture grown on sMEA. D) Representative micrograph of culture pre- and post- 30 percent stretch. E) Strain history of neurons under 30 percent strain. (Figure used with permission from the authors).

REFERENCES:

DiLeonardi, A. M., Matheis, E.A., Rafaels, K. A. . (2018). In vitro quantitative analysis of neuronal structural and functional changes following mechanical loading. Paper presented at the Neuroscience 2018, San Diego, CA.

DiLeonardi, A. M., Matheis, E.A., Rafaels, K. A. (2018). The Influence of Glia on the Neuronal Response to Mechanical Loading. Paper presented at the International Research Council on Biomechanics of Injury 2018 Conference, Athens, Greece.