News from the Collaborators

ZelosDx Collaborator Presents Data at a National Conference in June!

Deep Brain Stimulation can diminish diseases symptoms making it an effective therapy for a variety of neurologic disorders, including Parkinson's Disease, epilepsy, chronic pain, and depression. This technique involves the implantation of microelectrodes into specific regions of the brain followed by a continuous delivery of small electrical impulses to modulate the activity in the targeted brain area. The mechanism of action and several side effects are not well understood and remain an active area of investigation. In order to study the inflammatory response of the brain tissue to the electrode insertion and electro-stimulation, a rat model has been used to measure the amount of GFAP in peripheral blood phagocytes by both of the ZelosDx WINDOW INTO THE BRAIN blood tests. While these studies are still ongoing, the results so far have been very promising, showing an increase in this brain biomarker upon electrode implantation by ELISA as well as an increase in GFAP carrying phagocytes. https://neuromodulation.org/Default.aspx?TabID=719

Blood-test To Assess Inflammatory Biomarker GFAP In Peripheral Blood Monocytes Due To Chronic Brain Implants

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Introduction

- Immunohistochemistry is currently used to assess inflammatory responses to chronic implants in brain tissue
- Implant stimulation could exacerbate inflammation and cause tissue damage in a dose-dependent manner
- Glial fibrillary acidic protein (GFAP), expressed in reactive astrocytes, is a biomarker to assess brain tissue response to inflammatory stressors
- However, current methods to assess gliosis in chronic experiments are terminal as they require immunohistochemical analysis
- Peripheral blood monocytes (PBMCs) are recruited to the brain to clear inflammation debris and can re-enter the blood stream
- We report here results of an assay for trace amounts of brain-specific proteins in PBMCs
- We used this approach for the first time in rodents to make longitudinal measurements of GFAP in blood after chronic microelectrode array implantation and electrical stimulation

Methods

- We used the following 4 experimental conditions (n=3 rats in each condition implanted with 4 teflon-insulated tungsten electrode arrays) to assess GFAP levels in PBMC extracts:

  Condition 1. Surgery, craniotomy, no implant
  Condition 2. Surgery, implant, no electrical stimulation
  Condition 3. Surgery, implant, electrical stimulation, Stim1 - 9 nC/phase and 25 µC/cm² with a GSA of 35,000 µm² (below Shannon limit)
  Condition 4. Surgery, implant, electrical stimulation, Stim2 - 36 nC/phase and 1834 µC/cm² with a GSA of 1900 µm² (above Shannon limit)

- Each rat had ~1 ml of blood drawn 2 weeks before surgery, 72 hours after surgery, 2, 4, and 6 weeks after surgery, followed by a terminal bleed 10 weeks after surgery
- Cohorts in experimental conditions 3 & 4 were stimulated every day for 1 hr for the first 4 weeks
- Stimulation conditions were biphasic, charge-balanced at 100 Hz with amplitude of 180 µA and 50 µsec/phase (condition 3) or 360 µA and 100 µs/phase (condition 4)
- Blood samples were analyzed using single-sided ELISA assays for GFAP at ZelosDX, Tucson, AZ
- Electrical impedance spectroscopy (EIS) and cyclic voltammetry (CV) were performed periodically

Results

- Initial results showed 3- to 4-fold increase in GFAP expression between baseline and experimental condition 3 at 24 hours and 2 weeks post-implantation
- The levels of GFAP were found to decrease at 4-, 6-, and 10-weeks post-implantation
- Results of GFAP in PBMC extracts are consistent with terminal GFAP assessments in brain tissue
- Stimulation below the Shannon limit did not significantly impact GFAP levels
- EIS and CV measurements showed consistent electrode function during experiments

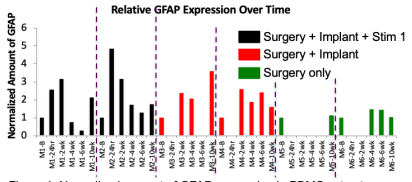

Figure 1: Normalized amount of GFAP expression in PBMC extracts over time under various conditions

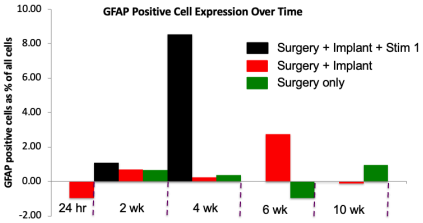

Figure 2: Percentage of GFAP positive cells (determined using FACS) over time under various conditions

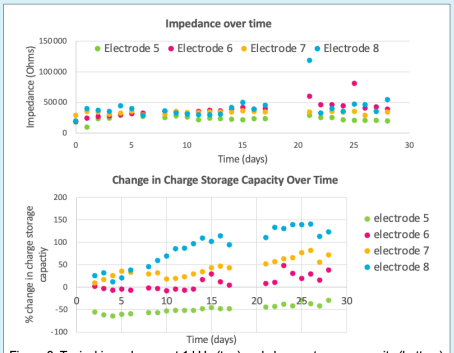

Figure 3: Typical impedances at 1 kHz (top) and charge storage capacity (bottom) in an array over the duration of a chronic experiment show no significant changes

- Electrical impedances at 1 kHz and charge storage capacities did not change significantly during the experiment indicating the integrity of the neural interface.
- The proposed novel assay involving PBMCs allows for multiple GFAP assessments at 2-week intervals in longitudinal experiments for the first time.
- This will allow us, for the first time, to track changes in expression of GFAP due to any interventions introduced during the experiment.

Conclusion

In conclusion, we have shown that the novel blood-based assay is capable of making longitudinal assessments of trace amounts of GFAP in rodent peripheral blood monocytes in chronic experiments. Changes in GFAP expression due to microelectrode implantation were consistent with prior studies using conventional terminal assessments.

Acknowledgements

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https://nsfbrain.org/sites/arizona-state-university/#

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