

Forensic Analysis of Retrieved Utah Electrode Arrays Following Implantation into Rat Cortex

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Statement of Purpose: Within the central nervous system, microelectrode arrays (MEAs) have the ability to record electrophysiological activity of single or small neuronal populations and have been used to translate volitional thoughts into functional outputs. The available evidence suggests that such devices have significant potential for a broad range of treatments including paralysis, amputation of extremities and debilitating neurological disorders. Unfortunately, widespread clinical implementation has been slowed due to inconsistent recordings and eventual failure, which is believed to be in part due to the brain's foreign body response (FBR) mounted against the implanted microelectrode. Using simple single penetrating device designs, our lab has shown that the FBR is a cell-mediated neuroinflammatory reaction associated with activated macrophages. It is believed the activated macrophages' soluble factor secretions influence brain tissue remodeling, WBC trafficking, BBB dysfunction and neuronal activity during the indwelling period. Despite the fact that the UEA is approved for human use, its FBR in animals and patients has been less well studied than other device types. To address this issue, our group has been studying the FBR and recording activity of 4 X 4 UEAs purchased from Blackrock Microsystems implanted in rat brain over chronic time periods.

Methods: Male Sprague Dawley rats (350g, N = 22) were anesthetized, placed in a stereotactic frame and a midline incision the length of the skull was made. Under stereotactic control, a 3 mm burr hole was drilled in the skull approximately 1.0 mm rostral to bregma and 1.5 mm laterally and lengthened as needed with a hand held dental drill. The UEA implanted in the primary motor cortex to a depth of 1 mm. Following indwelling period of between 2-6 weeks, rats were anesthetized and transcardially perfused with 100 mM PBS followed by 4% paraformaldehyde. Brains and electrodes were removed and postfixed with 4% paraformaldehyde for 24 hours and then placed in 30% sucrose until equilibration. Brains were horizontally sectioned at a 30 μ m thickness with a cyrostat. Sections were reacted with antisera against GFAP to visualize astrocytes, CD-68 for activated microglia and macrophages, IBA-1 for microglia, IgG for immunoglobulin G, Tomato Lectin (TL) for blood vessels, NF-160 for all neuronal processes, NF-200 for axons, and counterstained with DAPI. Sections were then mounted onto glass slides with Fluoromount-G. Retrieved electrodes were stained with CD-68 and DAPI. Fluorescent images were captured with upright (Nikon) and confocal (Olympus) microscopes. Lightfield corrections using primary controls were performed.

Results: In every case, we observed activation and recruitment of macrophages/microglia at the electrode/tissue interface. Further, retrieved devices

revealed ubiquitous attachment of activated macrophages/microglia on the device that was particularly dense at the base. Unique individual cases also existed within the cohort, suggesting that the amount of vascular damage could be quite variable with this sort of electrode array design. The analysis revealed that implanted devices provide a large surface area for macrophage/microglial attachment.

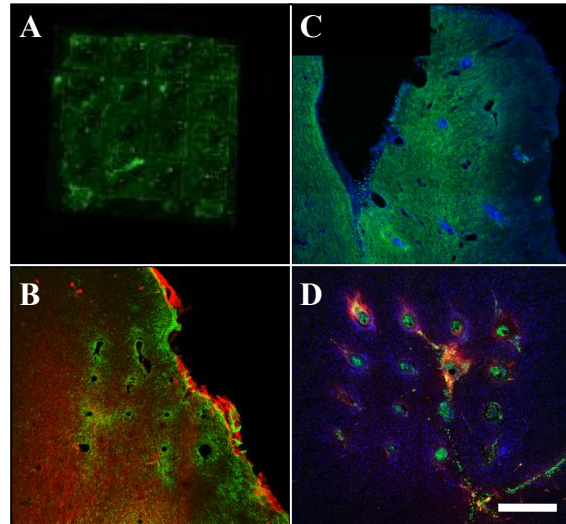


Figure 1. (A) UEA showing adherent CD68+ macrophages on device after chronic implantation in rat brain. (B):20 days, GFAP, NF-160. (C):15 days, NF-200, DAPI. (D):27 days, CD-68, IgG, IBA-1. The tissue reaction showed loss of myelin, astrocyte hypertrophy, neuronal loss, macrophage activation, and blood-brain barrier leakiness surrounding implants over the entire indwelling period. Scale bar = 500 μ m.

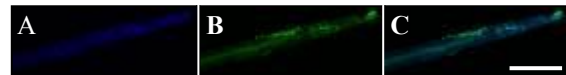


Figure 2. Images of the same explanted at 27 days as viewed with IHC. (A): DAPI. (B): CD-68. (C): DAPI, ED-1. The explanted electrodes displayed adhesion of activated macrophages to all implant surfaces as has been observe. Scale bar = 100 μ m.

Conclusions: This study showed that the tissue response associated with UEA is similar to the FBR of single shank monolithic devices. Explanted UEAs exhibited a layer of macrophages; which are believed to play a major role through their release of soluble pro-inflammatory chemokines and cytokines such as MCP-1 and TNF- α . These soluble factors may reach high local concentrations, remodel tissue and drive the FBR due to only one direction for diffusion at the device interface. This high relative abundance of macrophages may contribute to a high overall inflammatory burden. Fully understanding the characteristics of the FBR will allow for informed device design, which in turn may result in improved consistency and longevity.