The Foreign Body Response to Headstage Components adds to the Neuroinflammatory Burden of Indwelling Microelectrode Arrays

R. Smitty Oakes, Michael B. Christensen, Patrick A. Tresco.
Keck Center for Tissue Engineering, Department of Bioengineering, University of Utah, Salt Lake City, UT.

Statement of Purpose: Microelectrode arrays (MEAs) have successfully been used in neural prostheses for restoration of bodily functions through recording and stimulation of neuronal activity. However, poor functional longevity is a major hurdle in their clinical translation and has been, at least in part, attributed to the brain's foreign body response (FBR). While the FBR surrounding implanted MEAs has been well studied[1]; to our knowledge no group has studied the FBR to the other components used the anchor the array including the acrylic headstage and bone screws that are used to anchor the electrical connector to the cranium. To investigate this area, our group histologically analyzed the cortical cytoarchitecture underneath bone screws and other parts of the headstage. Additionally, explanted devices were assessed for adherence of activated macrophages.

Methods: *Animal Surgery* - Male Sprague-Dawley rats (225–250g), from three separate studies (n=32), were anesthetized under vapor anesthetic, Isoflurane, and a functional MEA was implanted stereotactically. For fixation, two types of screws were secured in the cranium; either stainless steel self-tapping bone screws (1.17mm, FST) or stainless steel blunt machine screws (1.85mm, Small Parts Inc.). Next, the implanted MEAs were fixed to the cranium using either custom fabricated polyurethane headstage, a medical-grade UV-curable acrylic, or a dental acrylic to cover the screws and connector. The skin was then sutured around the headstage leaving the electrical percutaneous connector exposed. *Euthanasia And Tissue Preparation* - Between 41 to 58 days postimplantation, animals were deeply anesthetized and transcardially perfused. Following perfusion fixation, intact neural prosthetics (including the skull, headstage, fixation screws, wires, and MEA) and brains were carefully dissected from tissue. Brains were post fixed overnight then equilibrated in 30% sucrose before sectioning. *Immunohistochemistry And Analysis* - Sections were analyzed using indirect immunohistochemistry (IHC) against GFAP for astrocyte hypertrophy and spatial distribution; NeuN to visualize neuronal nuclei; MAP-2 for dendrites; IBA-1 for macrophage morphology and spatial distribution; CD68 (ED1) for activated microglia/macrophages; RIP for myelination; Tomato Lectin for vascular morphology; and IgG for BBB disruption. Sections were counterstained with DAPI to identify nuclei and mounted with Fluormount-G. Confocal imaging was performed at 20x magnification, lightfield corrected, then stitched in photoshop.

Results: Results show that all components used for to allow neural recording from the brain elicit macrophage dominated FBR that in cases influences cytoarchitectural remodeling. This is most noticeable underneath bone screws which penetrate the cranium (Fig. 1B/D). Additionally, the explanted components exhibit a layer of proinflammatory CD68+ cells (Fig. 1C).

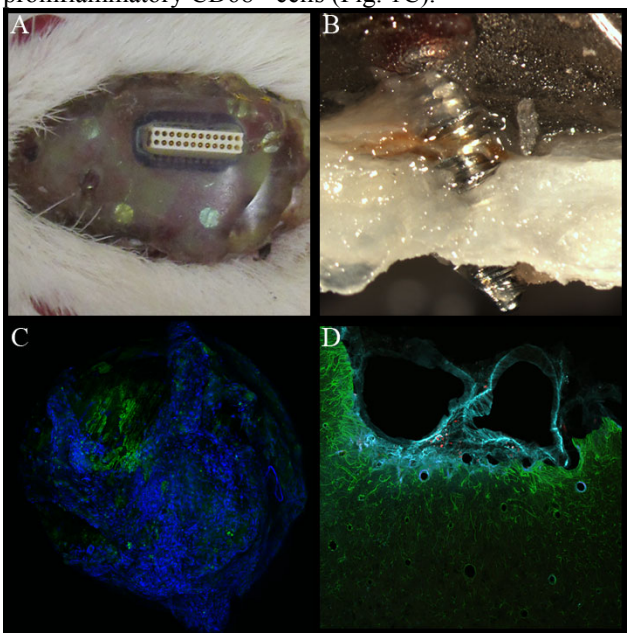

Figure 1. (A) Typical headstage used for chronic neural recordings in rats. (B) Stereoscopic image of an explanted headstage, showing a bone screw embedded in acrylic penetrating the cranium. (C) Following dissection, the components such as this representative screw are covered in a dense cell layer (DAPI) of proinflammatory CD68+ cells. (D) Representative horizontal section of FBR biomarkers show neuroinflammation (CD68), presence of serum proteins in brain parenchyma (IgG), and gliosis (GFAP) associated with bone screws used for fixation.

Conclusions: Our study indicates that all components of implanted neural prosthetics which contact tissue induce inflammation; thus contributing to the neuroinflammatory sequela beyond the electrode site[2]. Moreover, from the perspective of studying normal brain activity or from a patient care perspective the neuroinflammatory sequela should be minimized. A recent report showed that a chronic DBS implant in a similar animal model showed widespread and persistent neuroinflammation and associated cognitive deficits[3]. The broad impact of this neuroinflammatory burden may affect normal neuronal activity, plasticity and contribute to the poor device functionality and longevity. Additionally, neuronal pathologies may be induced; for example, epilepsy and cognitive dysfunction due to scar tissue formation.

References: **1.** (Polikov VS. J. Neuorsci. Meth. 2005;148:1-18) **2.** (Ekdahl CT. Proc. Nat. Acad. Sci. 2003;100: 13632–13637) **3.** (Hirshler YT. Exp. Neurol. 2010;222:42-50)