

BBB Leakiness is Associated with Recording Changes in Chronically Implanted UEAs

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Statement of Purpose: Microelectrode arrays offer the potential to record single unit activity from cortical neurons for the control of neuroprosthetic devices. The Utah Electrode Array (UEA) is a high density array with recording sites located at the tip of each tine. It is the only microelectrode array which is currently approved for human clinic trials. Despite its widespread use in electrophysiological studies, biocompatibility studies in rats do not exist. We have previously reported relationships between macrophage presence and blood-brain-barrier (BBB) dysfunction on electrode functionality by analyzing whole implant sites and comparing to electrophysiological metrics. Here, in an attempt to relate the FBR to device performance, we analyze individual recording site performance with histology.

Methods: 4x4 UEAs connected to Omnetics connectors were sterilized and implanted into the cortex of young male Sprague-Dawley rats (N=6). One week after implantation and at weekly intervals thereafter, electrophysiological recordings were obtained from freely moving animals. Single unit action potentials and associated signal-to-noise ratios (SNRs) were analyzed offline. Animals were sacrificed by transcardial perfusion following performance deficits. For histological analysis, 30 μm brain tissue sections were collected, evaluated for a battery of immunomarkers against neuronal cells and processes and inflammatory markers, and imaged microscopically. Quantitative measurements of biomarkers were performed by calculating the average pixel intensity in 50 and 100 μm radii around the recording site. Statistical comparisons were made using t-tests. P values below 0.05 were considered significant.

Results: A predictive modeling approach of small molecule clearance around the implanted UEA used by our group suggested that the FBR would be greater in the center of the array compared to the edges (Figure 1). Therefore, we compared electrophysiological metrics and histological markers over these general locations. We found that SNRs from center located electrodes were significantly lower than SNRs from electrodes located near the outside of the array (Figure 2). Case-by-case histological examination of the recording zones found differences in markers for IgG (BBB dysfunction), CD68 (activated macrophages/microglia), and GFAP (astrocytes), with edge electrodes always having lower average intensities of these markers.

Conclusions: This study shows that recording performance within a 4X4 UEA varies as a function of electrode location that is associated with changes in neuroinflammatory markers around recording sites. We found that sites with a lower inflammatory burden had significantly higher SNRs compared with those located at the center of the array. These results suggest that future designs should be based on decreasing the inflammatory

burden around recording sites, by increasing spacing, decreasing device surface area, and/or increasing small molecule clearance at the device base.

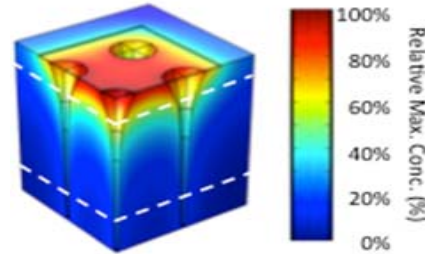


Figure 1: Modeling of pro-inflammatory small molecule diffusion predicts a larger FBR in the center of the UEA compared to the edges.

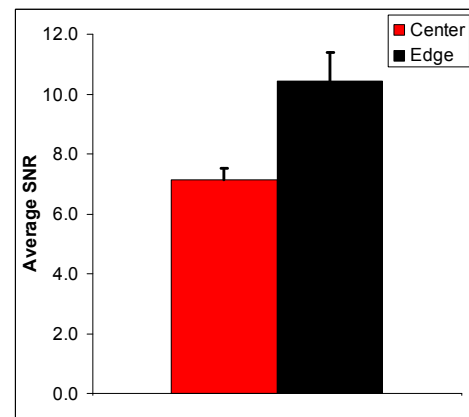


Figure 2: Average signal to noise ratios are significantly higher in recording sites located along the edge of the array compared with those located in the center.

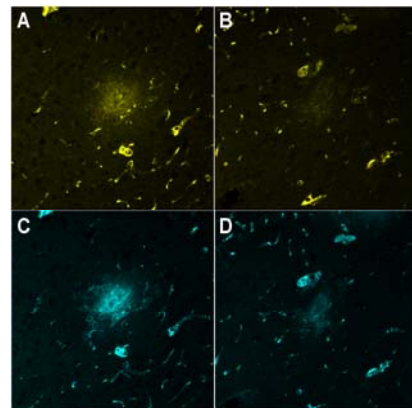


Figure 3: Representative images from recording sites located at the center of the array (A&C) and the edge of the array (B&D) for IgG (A&B) and CD68 (C&D). Sites at the edge of the array had significantly lower levels of both IgG and CD68 compared with center located recording sites.