Markers of BBB Leakiness Correlate with Single Unit Recording Performance in High Density Penetrating Electrode Arrays Implanted Chronically in Rat Motor Cortex

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Statement of Purpose: High density intracortical microelectrode arrays record the activity of neurons and are being used in a variety of research and neuroprosthetic applications. At present, however, such devices perform inconsistently at chronic time points. It is believed that the foreign body response (FBR) and the associated inflammation, gliosis, and neural degeneration are responsible for inconsistent performance, but few studies have directly examined the mechanisms. Furthermore, few studies have examined the FBR to high density, clinically-relevant devices in rat models. In this study, we characterized the FBR to the Utah Electrode Array (UEA) in rat motor cortex and examined relationships between the FBR and single unit recording performance.

Methods: 4X4 UEAs (Blackrock Microsystems, Salt Lake City, UT) were implanted into the motor cortex of 28 young adult male Sprague-Dawley rats. Three additional rats were implanted with a device for two minutes as a stab wound injury model. Every week, five minute long recordings were obtained from awake, unrestrained animals. Single unit action potentials were isolated via thresholding and principle component analysis using Offline Sorter (Plexon Inc., Dallas, TX). At time points between 2 and 12 weeks post-implantation, rats were perfused transcardially and their brains post-fixed for 24 h in 4% paraformaldehyde. The relative intensity and spatial distribution of cell nuclei, axons, macrophages, activated macrophages, blood-brain barrier (BBB) leakage (IgG), and astrocyte cytoskeletonal markers were evaluated using immunohistochemical methods.

Results: The number of single unit action potentials decreased by 49% from the first to the last recording sessions ($p = .0002$). The average signal to noise ratio (SNR) likewise decreased by 17% ($p = 0.01$), however this decrease was significantly greater for center electrodes than for edge electrodes. Quantification of immuno-labelling revealed that microelectrodes in the center of the array had significantly greater levels of IgG within the recording zones compared with microelectrodes located on the edge of the array ($p = 0.0003$) (Figure 1). In histological sections, cavities of tissue loss were observed in superficial cortex under the base of the array. The cavities varied in size and shape and often included the recording zones. Meanwhile, electrodes further away from cavities exhibited typical hallmarks of the FBR to single microwires and single-shank planar electrodes [1][2]. Electrode tips located in normal brain tissue significantly outperformed electrode tips associated with cavities. At the last session, 10% of electrodes in brain tissue were able to record action potentials, compared to 1% for electrodes in cavities, a statistically significant difference ($p = 0.01$). Stab wound injury animals showed similar cavities of tissue loss, albeit with less inflammation compared to animals with implants.

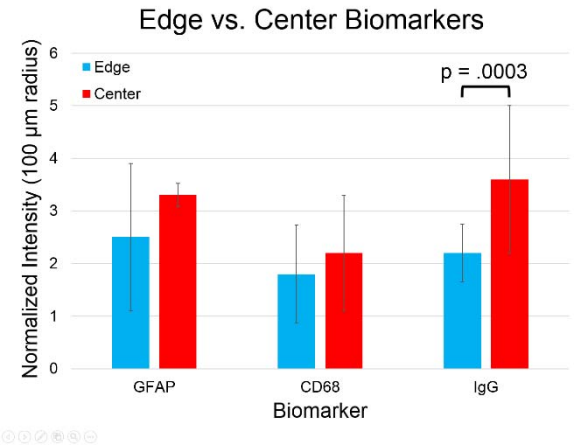

Figure 1. Quantification of biomarkers shows that center electrodes had significantly more IgG present in the recording zone than those located at the edge of the UEA.

Conclusions: We found that recording performance for center electrodes degraded to significantly lower SNR values compared to electrodes located at the edge of the 4X4 array. Moreover, this was related to greater BBB leakage near center electrodes, as evidenced by increased presence of IgG. BBB leakage may then lead to an unfavorable environment for neuronal function, increasing the distance between the recording site and the nearest healthy neuron and lowering the SNR as well as remodeling tissue. The FBR to the UEA was similar to single microwire or single shank planar electrodes except for the formation of a cavity of tissue loss in more superficial cortex. Such cavities have been reported in experimentally-induced infarction of multiple blood vessels in close proximity [3]. The presence of cavities in stab wound injured animals confirms that vascular injury is the most likely mechanism responsible for these areas of tissue loss. The architecture of the UEA, which has numerous closely-spaced microelectrodes inserted simultaneously into cortex similar to other devices of its type, has a much greater potential for vascular damage than single shank devices. Electrodes located near cavities performed poorly, which is unsurprising considering cavities were devoid of neural tissue markers. Together, these results suggest that strategies to reduce BBB leakage and vascular damage would improve the chronic recording function of high density intracortical microelectrode arrays.

References:

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[2] Winslow BD Biomaterials 2010 Mar;31(7):1558-67
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