Intracortical Electrodes of Different Material, Shape, Size and Tethering Induce Differential Inflammatory Responses that Significantly Impact Chronic Electrode Function.

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Statement of Purpose: Neural interfacing is a promising technology with clinical applications for the treatment of central nervous system (CNS) injuries and other debilitating neural diseases. Intracortical electrode implant performance however degrades with time, ultimately resulting in chronic electrode failure. The dominant hypotheses in this field imply that chronic electrode failure occurs due to either (a) insertion-associated injury to neurons, (b) chronic presence of a foreign material; (c) mechanical mismatch between the stiffness of the electrode and the brain; or (d) astro-glial scar electrically isolating the implanted electrodes from neurons. In this study we compared function of electrodes of different material, shape, size and tethering using a sensory evoked rat barrel cortex implantation model, and investigated the tissue response to these implants using histology and cytokine array analysis.

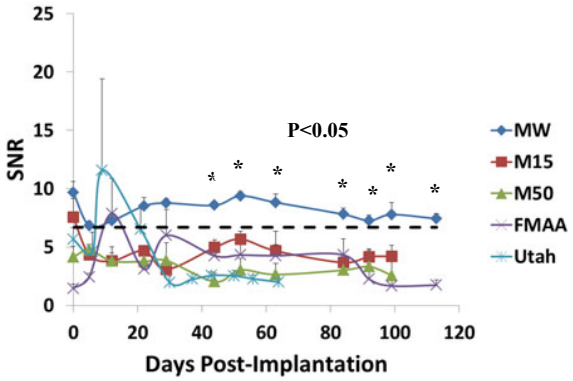

Figure 1. Signal to noise ratios (SNR) of electrophysiological recordings obtained from rats (n=4 each) implanted with electrodes of varying material, shape, size and stiffness over a period of 16 weeks.

Methods: We conducted histological analysis (n=6 each) of animals implanted with non-functional 15µm (tethered –MT; and untethered –M15) and 50µm (M50) thickness silicon planar electrode arrays, 75µm platinum/iridium floating microwire arrays (FMAA – fast tapered; and FMAB – slow tapered), and 50µm tungsten microwire (MW) arrays; and cytokine array analysis (n=4) of animals implanted with M15, M50, MW, FMAA and MW, over 3 days (3D) and 12 weeks post-implantation (12 WPI). A refined set of functional electrodes consisting of M15, M50, FMAA and MW electrodes (n=4 each) were subsequently compared to the clinical 'gold standard'– Utah arrays (n=4), and functional performance was evaluated in a sensory evoked rat barrel cortex model over a period of 16 weeks.

Results: In order to evaluate the foreign body response triggered by the implantation of intracortical electrodes of different material, shape, size and tethering, we conducted histological analyses using markers for glial scarring (reactive astrocyte marker-GFAP, reactive microglia/macrophage marker-CD68, fibroblast marker - vimentin), blood-brain-barrier breach (serum IgG), and neuronal viability (NeuN). Analysis of integrated fluorescence intensities from a distance of 50µm from the implant site, and measurements of the rate of decay of fluorescence intensities using an stretched exponential curve fitting model, indicated that MT electrodes showed significantly ($p<0.01$) higher glial scarring as marked by CD68 and vimentin expression at the end of both 3D and 12WPI when compared to M15 (untethered) electrodes. MW electrodes showed no significant differences in glial scarring between 3DPI and 12WPI when compared to all electrodes. No other significant differences were observed across other markers and electrodes from histological analysis. Cytokine array analysis of tissue surrounding electrode implants indicated that M15 and M50 electrodes induced significantly ($p<0.01$) higher expression of pro-inflammatory and neurotoxic cytokines as marked by increase in expression of Interleukin (IL) and tumor necrosis factor (TNF) superfamily members when compared to FMAA and MW electrodes at both 3D and 12WPI. Overall, MW electrodes induce a significantly ($p<0.05$) lower inflammatory response when compared to all other electrodes. Functional viability of implanted intracortical electrodes of different material, shape, size and tethering, as evaluated using a whisker stimulated sensory evoked cortical response assay indicated significantly ($p<0.05$) higher SNRs for MW electrodes when compared to all other electrodes chronically. Significantly, M15 and M50 silicon electrodes; and FMAA and Utah floating electrodes failed ~10 days post implantation.

Conclusions: Histological analysis of tissue surrounding intracortical electrode implants revealed few significant differences indicating that it is capable of identifying only gross differences and not subtle differences that can explain the differential functional behavior of electrodes. Cytokine array analysis provided a quantitative assessment of inflammatory and neurotoxic cytokines prevailing in the milieu surrounding intracortical electrode implants temporally. Results from these assays indicate that expression levels of pro-inflammatory ILs and TNF family members could serve as markers to predict intracortical electrode performance chronically.

Acknowledgements: This work was funded by the Defense Advanced Research Projects Agency (DARPA) MTO under the auspices of Dr. Jack Judy through the Space and NavalWarfare Systems Center, Pacific Grant/Contract No. N66001- 11-1-4014.