Chronic Blood Brain Barrier Breach Contributes to Intracortical Electrode Recording Failure

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Statement of Purpose: Ranging from retinal prosthesis to deep brain stimulators, the use of cortical electrodes is on the rise. However, while the feasibility of stable recording from the cortex has been demonstrated in humans, reliable long term recordings remain challenging due to unpredictable and diminishing performance over time. The predominant hypothesis has been that astroglial scar surrounding the implanted electrodes contributes to recording failure. However, there exists a temporal disconnect as the scar stabilizes well before the onset of recording failure. It is well established that disruption of the blood-brain barrier (BBB) contributes significantly to the progression of neurodegenerative disorders. However, the status of the BBB around implanted electrodes and its implication for electrode function has not been investigated. The goal of this study was to ascertain the status of the BBB around intracortical electrodes and determine the sequelae of a chronic BBB breach on neuronal health and inflammation around electrode implant sites.

Methods: Adult male Sprague Dawley rats were implanted with commercially available intracortical electrode arrays (microwire arrays [**MWT**], and Michigan silicon planar [**MS**]). Electrodes were implanted in the left barrel cortex. Evoked electrophysiological recordings (upon whisker stimulation) were obtained for a period of 16 weeks post-implantation (WPI). The permeability of the BBB was monitored non-invasively using fluorescent molecular tomography (FMT). Reactive gliosis, BBB disruption, and myeloid cell infiltration were assessed using standard immunohistochemical methods. To assess transcript levels of genes encoding for pro-inflammatory cytokines around electrode implant sites, the quantitative real time polymerase chain reaction (q-RT PCR) method was employed. All animals were sacrificed at 16WPI.

Results: Our results show that (i) MWT electrodes significantly outperform MS electrodes electrophysiologically; (ii) MS electrodes induced a significantly larger BBB breach (Figure 1) in comparison with MWT electrodes (iii) electrode implants lead to a chronically open BBB; (iv) we can non-invasively monitor BBB breach around electrode implant sites; (v) there is a direct correlation of extent of BBB breach to electrode function; (vi) increased BBB permeability causes localized inflammation and infiltration of antigen presenting cells and cytokines that further augment and mediate inflammation; and (vii) MWT electrodes which showed superior functional ability over chronic time periods, had a significantly enhanced wound healing response.

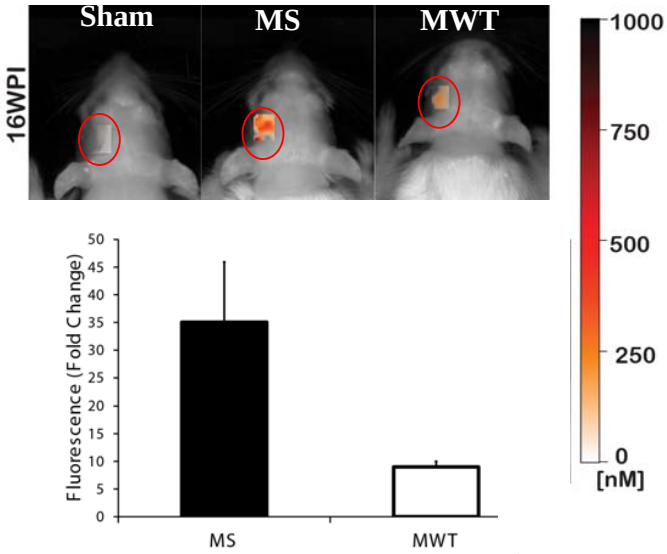

Figure1. Non-invasive imaging of the BBB at 16WPI using FMT. Left panel *sham* animals, middle panel *MS* implants, right panel *MWT* implants. Implant sites are circled in red. Fluorescence is quantified (n=4/group) and normalized to sham animals. Data are shown as mean± SEM. MS electrodes showed a significantly higher breach of the BBB than MWT electrodes at 16WPI ($p<0.01$).

Conclusions: While previous studies[1,2] have evaluated the tissue response to single shank electrode implants histologically, the physiological response of brain tissue to the more germane multi-electrode arrays, and the functional consequences of a chronically breached BBB have hitherto not been evaluated. Here we investigated the acute and chronic consequences of implanting intracortical multi-electrode arrays, and established the relationship between BBB disruption and intracortical recording electrode function. We also demonstrate that electrodes that fail chronically have a highly permeable BBB leading to an increased presence of active inflammatory cells and neurotoxic factors, whereas electrodes that perform better have significantly better healing of the wound and BBB breach. This data identifies BBB permeability as a critical physiological determinant of intracortical electrode function and may inform future electrode design and biochemical intervention strategies to enhance the longevity of implanted cortical electrode recordings.

References: 1) Potter KA et al., *J Neural Eng.* Aug 2012;9(4):046020. 2) Winslow BD et al., *Biomaterials.* Dec 2010;31(35):9163-9172.
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