Introduction
Understanding the potential contribution of strain to chronic recording failure is essential to the long-term use of electrode implants. Our lab has previously demonstrated that a mismatch in electrode stiffness and design can potentially lead to increased strain and inflammation. It is therefore clearly important to understand the biochemical milieu surrounding the electrode-host interface and study the response of glial cells to low strain fields in order to design biochemically compatible electrodes. In this study we hypothesized that chronic inflammation triggered by the persistent micromotion of implanted electrodes is brought about by strain induced inflammation. We tested this hypothesis by subjecting astrocytes and microglia (astroglia) to bi-axial cyclic strain using a stretch device and compared gene expression of CSPGs and cytokines between stretched and un-stretched astroglial cultures. The effects of stretch were functionally assayed by presenting conditioned media (CM) from stretched and un-stretched astroglia to primary rat embryonic day 18 (E18) cortical neurons.

Materials and Methods
Astrocytes and microglia were extracted according to methods previously described. Reactive astrocytes and microglia were plated on sterile plasma treated silicone sheeting and subjected to a ~5% strain at the rate of 1.42Hz for 16 hours at 37ºC, 5% CO2 and 95% humidity. After completion of the stretch regimen, CM from stretched and un-stretched astroglial cultures were collected and adsorbed on poly-D-Lysine coated coveslips for functional assays with rat E18 cortical neurons. Astroglial cell pellets were used for extraction of total RNA and analysis of gene expression using rat common cytokine PCR arrays (SABiosciences, Fredrick, MD). Differences >2 fold were considered significant.

Results
Results from the analysis of gene expression (Fig.1) show the up-regulation of the CSPG Neurocan along with several cytokines including members of the TGFβ, IL, IFN and TNF families, indicating a selective temporal response to induced strain. Inhibition of rat E18 cortical neurons cultured surfaces coated with CM from stretched cells is most likely due the elevated expression of Neurocan. We anticipate that lowering electrode induced strain coupled with local delivery of anti-scarring and immune-modulatory agents will lead to improved electrode design and functionality.

Discussion and Conclusions
The high mechanical stiffness of silicon microelectrodes induces scarring of neural tissue, ultimately leading to loss of function. Little is known about the biochemical outcomes of electrode induced strain on astrocytes and microglia. In this study we subjected astroglia to cyclic strain using a stretch device and studied its effects on astroglial secretions and gene regulation. Gene expression analysis of stretched astroglia showed immediate upregulation of the inhibitory CSPG Neurocan along with several cytokines including members of the TGFβ, IL, IFN and TNF families, indicating a selective temporal response to induced strain. Inhibition of rat E18 cortical neurons cultured surfaces coated with CM from stretched cells is most likely due the elevated expression of Neurocan. We anticipate that lowering electrode induced strain coupled with local delivery of anti-scarring and immune-modulatory agents will lead to improved electrode design and functionality.

References

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