Neuronal Activity-Dependent DNA Repair in Healthy Aging
Elizabeth Pollina, Ph.D. (year 1)

Neuronal Activity-Dependent DNA Repair in Healthy Aging

Abstract
Across a lifetime, neurons must retain a remarkable level of plasticity that facilitates learning, memory, and behavior. As animals encounter new sensory stimuli and learn complex behaviors, these experiences trigger changes in the activation of state of neurons in brains. In turn, increased neuronal activity induces the transcription of thousands of genes, the products of which dynamically modify the cells and circuits of the brain.

Neuronal activity-induced transcription is, however, a costly and risky endeavor. During transcription, the DNA is cut, unwound, and eventually resealed in a process that has the potential to create permanent mutations. How, then, do animals balance the benefits of elevated neuronal activity for plasticity with the risks it poses to the stability of their genetic code?

The goal of this proposal is to identify the molecular mechanisms that protect neuronal genomes from damage during periods of heightened neuronal activity. The proposal has two aims:

- Aim 1: we will use mouse models to identify the burden of mutations that accrue during aging at activity-induced genes in different types of brain cells. These studies will identify the cell types most susceptible to damage and will highlight gene candidates with high levels of damage that may contribute to age-associated cognitive decline.
- Aim 2: we will develop a platform for scalable, loss-of-function studies in human neurons to identify the protective factors that suppress damage and transcriptional dysfunction across long human lifespans.

Together, our work will provide foundational knowledge of how diverse neuronal cell types maintain transcriptional control and genome stability with age and how these genome control mechanisms go awry in aging and degenerative disease.