A new NASA-sponsored program project (NSCOR) has been organized to conduct the first comprehensive investigation of the response of a mammalian brain structure (mouse hippocampus) to charged-particle radiation. The NSCOR collaboration has three main goals. The first major goal is to quantify the time-and-dose-dependent changes in cellular composition and architecture. Stereological analysis of serial tissue sections on preserved brains will be used to quantify population changes in neurons, glia, and vascular endothelial cells out to two years after irradiation with accelerated protons and iron ions. To further characterize changes in vasculature architecture a polymer infusion technique (corrosion casting) will be used to produce a three-dimensional vasculature cast that then will be mapped by X-ray tomography to determine topological changes. Stem cells in the subgranular layer of the hippocampus will be identified by uptake of BrdUTP as they divide, migrate and reintegrate with adjacent hippocampal structures post irradiation. The second goal is to quantify hippocampal function(s). The primary measurement of function will be extracellular electrical recordings from hippocampal “brain slices” that reflect underlying functions such as connectivity, action potential generation & conduction, as well as neurotransmitter formation, secretion, and uptake. Two non-invasive methods will evaluate brain function and the evolution of changes with time. Electroencephalograms will map macroscopic spontaneous electrical activity while two state-of-the-art MRI magnetization sequences will visualize and quantify local oxygen utilization and white matter fiber tracts structural integrity. To quantify the brains’ overall performance under stress, animals will receive a systemic shock mediated by the immune system in the form of a reaction to lipopolysaccharide. Patterns of glial cell activation and cytokine production will address the level and character of the resulting inflammatory response while the functional perturbations will be assessed by electrophysiology. A complementary objective will employ the APP23 transgenic mouse that develops the pathological changes associated with Alzheimer’s disease. Measurements of irradiated mice will determine whether radiation exposure affects the latency and severity of the disease-associated pathological changes. System performance in the APP23 tg mice will once again be assessed by electrophysiology. To further characterize Alzheimer-like changes, corrosion casting will be used to determine vascular topological changes, and microscopic infarcts associated with amyloid protein deposits. The third major goal is to quantify molecular markers that underly cellular and system changes. The team will quantify the frequency and structural spectrum of mutations in hippocampal samples using the E. coli β-galactosidase gene present in a transgenic mouse’s tissues. Finally, by using transcription profiling hybridization, the status of a set of 96 genes involved in cytokine signaling during inflammation will be assessed. The following figure provides an orientation to the structure of the mouse hippocampus (A) and conceptions of the anatomical sampling (B) and electrophysiological recordings that will be used (C).

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**Fig. 1:** Schematics of the rodent hippocampus. A) This schematic reveals the location and extent of the hippocampal formation in the rodent. A coronal slice through the septal pole of the hippocampus is shown in the expanded histological section (CA=cornu Ammonus, H=hilus). B) This schematic illustrates the immunohistological usage of mouse hippocampus. C) This coronal hippocampal schematic illustrates all of the primary cell types and their connectivity. It also illustrates electrophysiological recording sites within the CA1 and dentate gyrus (DG). (SC=Schaefller collaterals, mf=mossy fibers, pp=perforant path).