The hippocampal dentate gyrus (DG) is the only area in the adult human brain that continually exhibits neurogenesis, the formation of new neurons from stem and progenitor cells. In spite of extensive research, little is known about how adult neurogenesis contributes to hippocampal function. We contend that insight regarding this fundamental issue can be gained by deepening our understanding of how newborn neurons develop and integrate into existing brain circuitry. The present lack of techniques for visualizing in the intact brain the newborn hippocampal neurons over their developmental time scales of weeks has stymied the investigation of fundamental questions such as: When, if ever, in their life course do newborn neurons attain structural stability? To what extent do the massive events of cell proliferation, migration, and cell death that are part of adult neurogenesis impact the circuit organization of the previously existing neurons? How do an animal's age and physical activity level, both regulators of adult neurogenesis, influence these dynamic processes? In this work we will address this pressing need for a method capable of imaging adult hippocampal neurogenesis in the live brain. We plan to capitalize on recent technological advances in time-lapse optical microendoscopy, a novel methodology for imaging cells over weeks and months deep within tissue. The goals of our research are thus to: (1) Develop a chronic mouse preparation for time-lapse in vivo microendoscopy imaging of adult hippocampal neurogenesis in the DG over weeks and months. Our approach uses: (a) Optical microendoscopes for imaging cells deep in the brain;(b) A chronic mouse preparation for time-lapse microendoscopy in the DG;(c) Transgenic mice and viral vectors to express fluorescent proteins in neural progenitors and newborn neurons. Together, these tools will permit longitudinal, high-resolution two-photon imaging of cells'detailed morphologies for progenitor cells, and new and mature neurons in the live adult DG. (2) Characterize the development and structural plasticity of neurons in the adult DG. We will assess how newborn cells'development and structural dynamics are affected by an animal's age and physical activity, by measuring the growth or retraction of newborn neurons'dendritic branch tips, the branching complexity of their dendritic trees as a function of developmental time, and distances and rates of cell migration from the sub-granular to the granular layer. We will compare these parameters between young adult and aged mice, under baseline conditions and in mice permitted voluntary exercise. We will also assess to what extent structural dynamics occurs in mature DG neurons and depends on an animal's age and physical activity. Our study will thus yield initial glimpses of developing neurons in the live adult hippocampus and address some key unanswered questions about how newborn neurons integrate into the DG network in adulthood and aging.

Public Health Relevance

The hippocampus, a brain structure important for learning and memory, is the only area in the human adult brain that continually exhibits neurogenesis, the formation of new neurons from stem and progenitor cells. Adult hippocampal neurogenesis declines during aging, and defects in neurogenesis have been implicated in many neuropsychiatric disorders, including epilepsy, depression, schizophrenia, and Alzheimer's disease. The goals of our work are to develop a novel imaging technology for directly visualizing adult hippocampal neurogenesis in living mice, and then to use this technology to examine how newborn neuron development differs between the hippocampi of young adult and mice, towards identifying specific developmental stages as potential therapeutic targets for future interventions.