The over-arching goal of my current research is to understand how the immune system interacts with the brain during both the sensitive period of neural development and adulthood. Specifically, my interest is how these interactions affect the normal function of the hippocampus in learning and memory. The immune system is a critical interface between the external world and our internal physiology. External stimuli can directly affect the immune and endocrine systems and via these systems affect the brain's development and later-life function. The effects of interactions between the nervous and immune systems during development are often profound and enduring given the critical roles of the resident immune cells of the brain, microglia, and their releasable factors, cytokines and chemokines, in many processes of neural development. Microglia and their signaling molecules affect adult learning and memory processes as well. The hippocampus, in particular, is a highly plastic region that is particularly sensitive to immune disruption and inflammation. To build on my current doctoral work, my future research goals are the following: explore novel insights into the function of the immune system within the brain and its effects on behavior, identify the unexplored role of immune molecules as neuromodulators, discover a novel role for immune cells and molecules in the plasticity of circuits underlying learning and memory that respond to enriching external stimuli, and explore the developmental events with direct neuroimmune and neural function for the life of the individual.

My background and training provide me with a deep understanding of interactions between the nervous and immune systems and the effects of immune stimulation on neural development and adult neural function. My range of techniques extends from preparation of primary neuronal/glial cultures to the analysis of gene expression and protein expression in discrete brain regions to a range of behavioral assays and surgeries. I have trained many undergraduate students on these techniques, allowing them to participate in data collection during various parts of an ongoing experiment. Thus, I am able to ask specific short-term and long-term mechanistic questions regarding neuronal and glial function from a developmental perspective, while being able to test these mechanisms and their effects on behavior in adulthood with extensive undergraduate participation in the process.

Doctoral Research

In July 2009 I joined the laboratory of Dr. Staci Bilbo at Duke University for my doctoral training. Her interest in the effects of the immune system on the brain extended my interest in examining the brain as a part of the "whole animal" in which external stimuli can have profound implications for brain function. During my doctoral studies in her laboratory, I have examined the hippocampus as a critical and unique neural substrate for learning and memory. In particular, I have sought to understand how immune signaling in both the normal and disordered brain affects hippocampal function.

The hippocampus is a region with remarkable potential for plasticity as well as a marked vulnerability to perturbations. Microglia and immune signaling molecules have significant effects on both hippocampal attributes and may be the key bridge between these qualities.

Fundamental Findings from My Dissertation Experiments:

1. **Neonatal infection with *Escherichia coli* causes enduring changes in microglia reactivity into adulthood.** A single infection in early life (postnatal day 4) alters microglia, such that they are more reactive at baseline as well as more responsive to immune stimulation in culture. They show a larger, more reactive morphology in the adult brain, especially in the hippocampus.

2. **Neonatally infected rats that are given a second immune challenge in adulthood ("two-hit" rats) have significantly impaired hippocampal-dependent memory on a fear conditioning task.** Neonatal infection alone does not produce cognitive deficits in adulthood, but a second *in vivo* immune challenge "unmasks" a deficit in contextual fear conditioning and context pre-exposure. The learning impairment is specific to the hippocampus because the "two-hit" rats are not impaired during a fear conditioning tone test that is reliant on the amygdala.

3. **Exaggerated expression of interleukin-1β (IL-1β), a cytokine required for learning, during fear conditioning is the cause of the impairment in the "two-hit" rats.** Two hours following contextual fear conditioning, during memory consolidation, all rats express IL-1β in the hippocampus. "Two-hit" rats, however, express exaggerated IL-1β at the 2 hour time point. Blocking IL-1β production during the consolidation period with caspase-1 inhibitors or minocycline, a known microglia inhibitor, eliminates the cognitive impairment in the "two-hit" rats.

4. **Neonatal infection impairs flexibility for a reversal task on a Morris water maze task and alters neural network expression within the dentate gyrus (DG) of the hippocampus following a memory test.** In adulthood, neonatally infected rats acquire a water maze location more quickly than controls and their improved memory is correlated with reduced neuronal activation in the DG. However, the neonatally infected rats have memory impairments on a reversal task in the Morris water maze in which the platform is moved to a new location. All rats learn the new platform location in the same number of trials. When tested for memory of the new platform with the platform removed from the maze, neonatally infected rats do not demonstrate a memory for the new location while controls do.

5. **Environmental enrichment markedly reduces the inflammatory response within the hippocampus after an immune challenge.** Home cage controls have a robust pro-inflammatory response within the hippocampus, expressing many cytokines and chemokines. Rats that had 7 weeks of environmental enrichment, however, have an attenuated expression of a subset of pro-inflammatory molecules, and this attenuated response occurs exclusively within the hippocampus, and not in adjacent cortex. Microglial and astrocytic marker density is also increased in the hippocampi of enriched rats, indicating a possible change in morphology in these cell types.

Long-term Interests and Research Goals:

- Can we elucidate the molecular mechanisms by which environmental enrichment alters the response of microglia to an immune challenge? Are there specific cellular relationships, such as interactions between neurons and microglia, which are changed by enrichment? Cell culture experiments, using an *ex vivo* approach, would assess specific populations of cells and the effects of environmental enrichment on their phenotype.

- Can we better understand the effects of environmental enrichment on developmentally-mediated nervous system changes, especially in the case of the neonatal infection model?

- Others in the Bilbo laboratory have determined that sex differences exist in the colonization and function of microglia throughout development of the rat brain (Schwarz et al., 2012; *J Neurochem*). All of the data for the neonatal infection model has been characterized in males, but much of the environmental enrichment literature uses females almost exclusively. How do potential sex differences in the effectiveness of environmental enrichment mediate the response of microglia to inflammation or other neural disorders?

- Neonatal infection, prenatal infection and other types of inflammation during development are thought to influence the prevalence and severity of neuropsychiatric disorders. How might neonatal infection influence signaling by neuromodulators to influence the development of neural pathologies?