**October 22, 2019 (Tuesday)**

**Below is the prompt for the Personal, Relevant Background and Future Goals Statement:**

**Please outline your educational and professional development plans and career goals. How do you envision graduate school preparing you for a career that allows you to contribute to expanding scientific understanding as well as broadly benefit society? Page limit - 3 pages**

**Describe your personal, educational and/or professional experiences that motivate your decision to pursue advanced study in science, technology, engineering or mathematics (STEM). Include specific examples of any research and/or professional activities in which you have participated. Present a concise description of the activities, highlight the results and discuss how these activities have prepared you to seek a graduate degree. Specify your role in the activity including the extent to which you worked independently and/or as part of a team. Describe the contributions of your activity to advancing knowledge in STEM fields as well as the potential for broader societal impacts (See Solicitation, Section VI, for more information about Broader Impacts).**

**NSF Fellows are expected to become globally engaged knowledge experts and leaders who can contribute significantly to research, education, and innovations in science and engineering. The purpose of this statement is to demonstrate your potential to satisfy this requirement. Your ideas and examples do not have to be confined necessarily to the discipline that you have chosen to pursue.**

**Important questions to ask yourself before writing the statement:**

1. **Why are you fascinated by your research area?**
2. **What examples of leadership skills and unique characteristics do you bring to your chosen field?**
3. **What personal and individual strengths do you have that make you a qualified applicant?**
4. **How will receiving the fellowship contribute to your career goals?**
5. **What are all of your applicable experiences?**
6. **For each experience, what were the key questions, methodology, findings, and conclusions?**
7. **Did you work in a team and/or independently?**
8. **How did you assist in the analysis of results?**
9. **How did your activities address the Intellectual Merit and Broader Impacts criteria?**

**Introduction:**

Memory and cognition are cornerstones of the human experience and are degraded by common neurological disorders such as Alzheimer’s and stroke. A comprehensive understanding of the complex interactions regarding memory encoding, consolidation, and retrieval remains elusive1. One major difficulty in elucidating the functions of these networks has been the brain’s immense interconnectivity; a single perturbation of a network can have a complex cascade of effects2. With novel technologies such as optogenetics and more sophisticated analytical techniques that assess connectivity and information flow between brain areas, we are now able to dissect the functional networks underlying memory formation more precisely than ever before.

Episodic memory is encoded through the cooperation of multiple brain regions, primarily hippocampal and parahippocampal areas. Ischemic stroke often impairs memory and cognition despite the absence of direct lesion to the hippocampus3 and has been used as a tool to interrogate spatial learning4. While the electrophysiological changes to memory formation following injury are poorly understood, optogenetics is a powerful tool that can be used to interrogate the activity of these neuronal networks.

Optogenetics allows high spatial and temporal control, and cell-type specific manipulation by virally rendering neurons sensitive to stimulation by light. Utilizing optogenetics will allow us to manipulate network activity during memory formation in real-time and observe the effects with electrophysiology and behavioral recordings.

**Proposed Research:**  In order to gain a more thorough understanding of the underlying electrophysiology of memory encoding, I plan to perturb memory formation in a rat model using a focal injury remote to the hippocampus and use targeted real-time optogenetic stimulation to see which features of the electrophysiology are most important to memory encoding by measuring change in spatial memory retention. There are two candidate features that I will be testing in this proposal. Sharp wave associated ripples (SPW-Rs) are known to encode memories, and phase-amplitude coupling (PAC) is a general framework to view information flow and connectivity between brain regions.

**Aim 1: Optogenetically lengthen SPW-Rs following stroke to augment memory encoding.**SPW-Rs are high frequency oscillations in the hippocampus related to memory encoding5. My previous work has shown that the decrease in memory function following stroke is correlated with shortened SPW-Rs6. Recent work has shown that naturally occurring long-duration SPW-Rs are associated with better memory performance, and that lengthening short-SPW-Rs optogenetically increases performance and recruits more diverse neuronal assemblies7. I hypothesize that by prolonging SPW-Rs following stroke, the more diverse neuronal assemblies recruited may project to a wider set of potentially healthy cortical tissue, which will allow for more successful encoding of memory. To test this, I will implement a closed-loop decoding algorithm to detect the occurrence of SPW-Rs in real-time during a behavioral task and use optogenetic stimulation to prolong SPW-Rs following stroke, elaborated below.

**Aim 2: Optogenetically induce PAC following stroke to augment memory encoding.** PAC is a method of measuring the interaction of local oscillations between brain regions8. The hippocampus has long been shown to coordinate function with theta (3-7 Hz)-gamma (30-60+ Hz) coupling9. Recently my work has shown that theta-gamma coupling exists between the hippocampus and regions as remote as sensorimotor cortex, and that theta-gamma coupling between the hippocampus and cortex break down following a focal ischemic stroke6. Recently, our lab has shown for the first time that PAC can be induced between two distant brain regions using optogenetic stimulation10. I hypothesize that optogenetically induced PAC will increase the relative potentiation between the two brain regions, facilitating an increase in communication. To test this, I will stimulate the cortex and hippocampus simultaneously during memory demanding periods, inducing coupling between theta (5 Hz) in the hippocampus and gamma (50 Hz) in the cortex. I will quantify the increase in communication using both electrophysiology recordings as well as behavioral metrics.

**Specific methods for both aims:** I will quantify the effects of manipulation using behavior and electrophysiology recordings during three memory demanding tasks: the M-maze test, the cheese board test, and a delayed non-match to sample test11. These tests utilize both egocentric and allocentric learning and vary memory demand by changing the inter-trial delays. Following training I will virally transfect rats with AAV5-CaMKIIa-hChR2(H134R)-EYFP —an optogenetic virus which encodes an excitatory opsin expressed in excitatory neurons— in the sensorimotor cortex and hippocampus. I will separate control and stroke groups, performing distal middle cerebral artery occlusion in the left hemisphere of the stroke group. I will implant four linear silicon μLED optrodes such that recordings from cortex and hippocampus are captured simultaneously from both hemispheres in both stroke and control groups. Rats will recover for one month post-operatively. Following recovery, I will split both stroke and control groups into three treatment groups with cohorts of ten rats each: no treatment, event-related stimulation, and random stimulation as a negative control. I will subject rats to tests for one month with optogenetic stimulation, collecting simultaneous electrophysiology recordings from the cortex and hippocampus, and motion capture to quantify behavioral outcomes.

**Expected challenges:** Because the effect remote injury has on the electrophysiology of the hippocampus is not well understood, how memory encoding features will react to optogenetic stimulation following stroke is difficult to predict. Regardless of the outcome, this novel work will reveal insights into how well memory formation networks are able to adapt to injury.

**Intellectual Merit:** SPW-Rs are a well-documented feature of memory encoding but modifying the characteristics of SPW-Rs with optogenetics has only recently begun to be explored. This work will be the first to attempt to modify SPW-Rs in a disease model to assess the potential for functional treatments.

Our group is the first to show that PAC can be induced through optogenetic stimulation [ref]. This work will be the first to use induced PAC to affect behavior, and to assess its ability to recover function in a disease model. PAC has been observed in multiple brain areas, including the basal ganglia and the neocortex, so this work can be translated to other brain regions as well.

**Broader Impact:** The precise neuromodulation achieved through optogenetic stimulation has the potential to fundamentally change the way we approach treatments to neurological disorders. Though there has been significant research into recovering motor function using optogenetics12, this work will be the first apply optogenetics to the cognitive sequelae following stroke. This research has direct clinical applications and will work well to supplement the active field of motor rehabilitation to create a more holistic therapy strategy. Research is already underway to develop a prosthetic hippocampus for humans13: it is not hard to imagine doctors prescribing a memory or cognitive prosthesis in the near future.

**References:** 1. Jenkins, T. A *et al.* J. Neurosci (2002). 2. Fernández-Ruiz, A. et al. Science (2019). 3. Harrison, L. M. *et al.* Behav. Brain Res. (1996). 4. Tort, A. *et al.* J. Neurophysiol. (2010). 5. Buzsáki, G. Neuron (2002). 6. Colgin, L. L. et al. Nature (2009). 7. **Ip, Z**. *et al*.Conf. Proc. …IEEE EMBC (2019). 8. Yazdan-Shahmorad, A. *et al.* Conf. Proc. ... IEEE Eng. Med. Biol. Soc. (2018). 9. Buzsáki, G (2015). 10. Hampson, R. E. et al J. Neural Eng. (2018)

**Title:** Memory Augmentation through cortico-hippocampal optogenetic stimulation in a

Optogenetic memory augmentation following ischemic lesion