PROJECT SUMMARY (See instructions):

Neuroscience has recently come into an “age of light”, whereby the activity of neurons and whole microcircuits can be recorded and stimulated with two-photon imaging and optogenetics, all while tracking an animal’s behavior. However, these powerful methods have not made their way into the primate which is the animal-model of choice for linking circuits to high-level cognitive tasks and decision-making. The long-term goals of this collaborative project are to provide primate physiologists with a toolbox for obtaining stable two-photon imaging (Aim 1) and optogenetic stimulation (Aim 2) of specific functional compartments and cell-types in the behaving primate. Furthermore, we will develop computational tools to interpret the acquired high-dimensional datasets (Aim 3). To expedite our achievement of these Aims, year 1 of the project, described in detail here, will be devoted to a streamlined version of the ultimate experimental preparation. For Aim 1, this entails chair-training head-fixed macaque monkeys that have been injected with an AAV-expressing calcium indicator to track signal quality and brain stability with wide-field imaging, followed by an acute experiment with two-photon imaging. The necessary expertise and equipment is already in-place to perform wide-field imaging of the calcium indicators (see preliminary data) along with two-photon imaging in the anesthetized preparation (Nauhaus et al 2012). In turn, this approach provides a valid test-bed for engineering solutions to each foreseeable problem that will be encountered with two-photon imaging in the behaving primate. These efforts include 1) the design of a recording chamber – objective lens configuration, 2) identifying the optimal viral serotypes, promoters, and time-points for maximizing signal intensity of calcium indicators, and 3) correcting for brain movement. Next, the goal of Aim 2 in year 1 is to design light stimulation protocols for evoking focal responses within unique compartments of the visual cortex. This is both a computational and optics problem to “map” patterns of focused light to patterns of cortical activity, with the ultimate goal of mapping patterns of activity to behavior in subsequent years of the project. Voltage-sensitive dye imaging, in both awake and anesthetized animals, will be used as a means of calibrating the light stimulation to achieve the desired pattern of cortical activity. Finally, our goal for Aim 3, in year 1 is to begin development of quantitative models that describe how pooled activity of many single neurons translates to the observed macroscopic signals obtained with wide-field imaging. Wide-field and two photon data in the anesthetized primate from Aim 1 will be used as the preliminary data set for testing these models.

RELEVANCE (See instructions):

This is a novel collaboration between three PIs at UT Austin. Each PI has experimental and computational expertise that is independently unique within neuroscience, with each playing a vital role in the proposed research. Dr. Seidemann has expertise in maintaining optical windows in the behaving primate to chronically image populations with VSD. His lab has recently capitalized on this methodology by performing the first wide-field high quality and stable imaging with genetically-encoded Ca^{2+} indicators (GCaMP6) in the behaving primate, which is a major stepping stone toward achieving two-photon imaging and optogenetic stimulation in the behaving animal. The Seidemann prep will also allow us to track the sustainability of new chamber designs and Ca^{2+} indicators. Next, Dr. Nauhaus has proficiency with 2-photon imaging in anesthetized primates. At this preliminary stage, the stability of the anesthetized preparation will be used to test tools for the eventual experiments with 2-photon imaging and optogenetics in behaving primates. Finally, Dr. Geisler is a renowned expert in models of neural coding that make predictions about the population activity derived from these very experiments. Taken together, this collaboration has the potential to develop a novel and widely applicable toolbox for optically monitoring and manipulating genetically-defined neural populations in the brain of behaving primates. The short-term goals outlined here capitalize on preexisting equipment and ideas to establish the groundwork for a more broad and ambitious research plan.