SPECIFIC AIMS: The overarching goal of this application is to develop neural stimulation strategies to manipulate and study functional neural circuits that mediate haptic perception and control.

Electrical microstimulation is a powerful tool to study the role of brain areas in perception and action, and, more recently, has been used to elicit artificial sensations in subjects controlling robotic arms[1-4]. Although this approach is promising, the widespread electrical effects of microstimulation limit selective control of distributed functional ensembles. Further, because microstimulation synchronizes activity across most cells within the stimulated region, it may lead to post-synaptic activations of different functional pathways that, in sum, generate ambiguous percepts. These shortcomings hinder the use of microstimulation to evoke complex tactile sensations (e.g., object shape and slip) mediated by sparse neural representations[5,6]. More recently, studies have turned to optogenetics, which provides spatially-localized and rapid control of cell-type specific (i.e., excitatory and/or inhibitory) neural circuits *in vivo*[7,8]. However, behavioral effects of optogenetic stimulation in large-brain animals (e.g., monkeys) have been mixed, likely because light fails to activate a sufficient portion of the neural circuit mediating the behavior[9,10]. To overcome these limitations, we will use combined microstimulation and optogenetics to provide robust and refined stimulation patterns that selectively activate functional circuits mediating behavior. In particular, we will use inhibitory optogenetics to suppress neurons inadvertently activated by microstimulation.

Neural stimulation strategies do not typically account for the brain's state at the moment of stimulation. Yet, sensory processing and behavior are selectively modulated by changes in the ongoing dynamics of neural population activity[11,12]. In particular, gamma-band amplitude (~30-100 Hz) correlates with behavior, and increases in brain areas encoding relevant stimuli[13,14]. Here, we will assay whether artificially-induced tactile sensations are enhanced when neural stimulation is applied during periods of high gamma-band activity.

Experimenter control of gamma activity can be a major asset to study how neural dynamics modulate sensory processing and behavior. Studies in mice show that 40Hz optogenetic drive of interneurons evokes gamma oscillations by imposing inhibitory effects in the network every ~10-30ms[15-18]. Yet, a dependable method to manipulate gamma-band activity in a primate brain has not been developed. We will use optogenetics in primate neocortex to selectively target interneurons, and test whether gamma oscillations are generated via similar inhibitory network mechanisms. Optogenetic control of gamma activity can enhance Brain-Machine-Interface (BMI) applications by ensuring that microstimulation is reliably applied during epochs of high gamma power.

Effective neural stimulation of functional circuits typically requires an exhaustive search within electrical and optical parameter spaces. We will use computational modeling to guide the physical qualities (e.g., intensity and frequency) and spatio-temporal stimulation patterns that optimally activate tactile circuits. Our approach is to inject viruses with optogenetic elements, and record neural activity in area 1 of somatosensory cortex in monkeys performing tactile discrimination tasks. Recordings, as well as optical and electrical stimulation, will be done using a transparent microelectrode array[19] positioned over the virally infected area. There are two specific aims.

Aim 1 – Evoke tactile motion sensations using optogenetics and microstimulation: We will test the hypothesis that combined electrical and optogenetic stimulation generates enhanced tactile motion percepts by synchronizing motion-tuned somatosensory ensembles. The mechanism of action is that microstimulation synchronizes cells within the stimulated area, including motion-tuned cells, whereas selective spatio-temporal patterns of inhibitory optogenetic stimulation suppress non-motion-tuned ensembles inadvertently activated by electrical stimulation. Further, we expect that neural stimulation effects will be enhanced during states of high gamma power. To test our hypotheses, we will train monkeys on a tactile motion direction discrimination task, and electrically and/or optogenetically stimulate tactile motion ensembles during different periods of gamma activity.

Aim 2 – Assay the role of interneurons in generating gamma oscillations in monkeys: We will test the hypothesis that gamma-band oscillations in primate brains are mediated by recurrent activation of an inhibitory interneuron network every ~10-30ms. We expect that optogenetically-induced gamma oscillations will lead to improvements in sensory processing and behavior by increasing synchronous spiking between neurons tuned for relevant features of a task. To test theses hypotheses, we will apply 40Hz optogenetic stimulation[15,17] to GABAergic interneurons in monkeys trained on a tactile motion discrimination task.

FUTURE GOALS: Data gathered from these aims will inform an R01 grant aimed at studying cross-cortical circuit dynamics underlying haptic perception in monkeys. This award will also help establish a translational research program focused on developing novel strategies to provide artificial sensations in BMI applications.