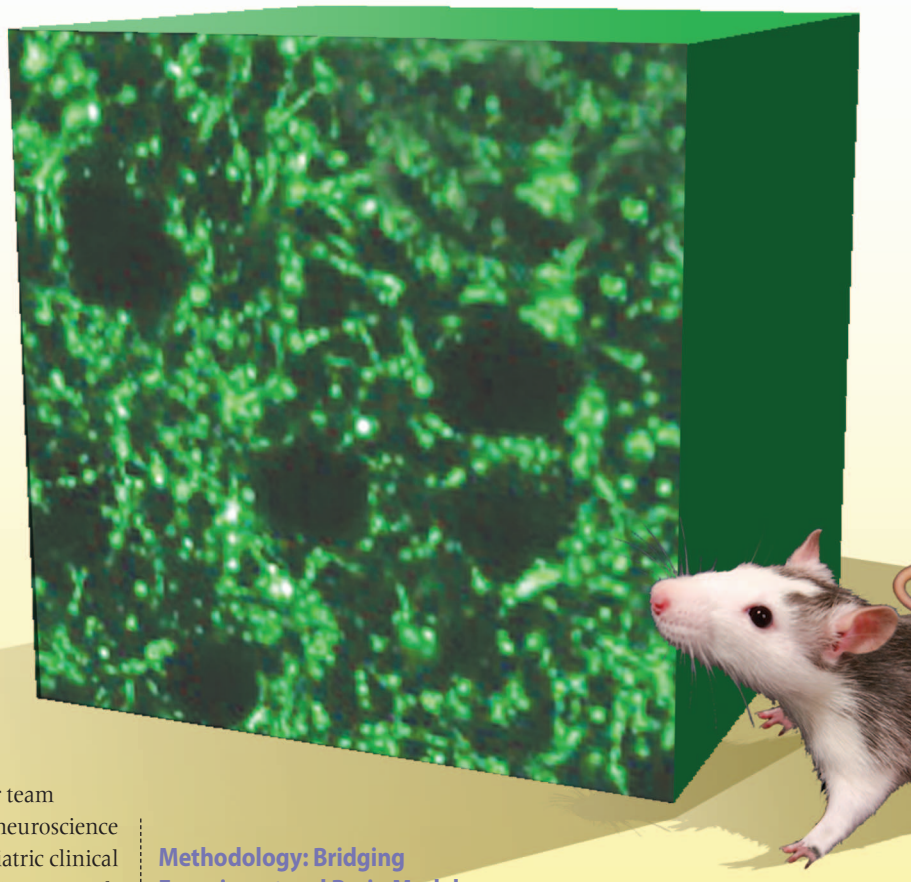
Brain Models Enabled by Next-Generation Neurotechnology

Using Multiscale and Multimodal Models

By Krishna V. Shenoy and Arto V. Nurmikko



As many articles in this issue of *IEEE Pulse* demonstrate, interfacing directly with the brain presents several fundamental challenges. These challenges reside at multiple levels and span many disciplines, ranging from the need to understand brain states at the level of neural circuits to creating technological innovations to facilitate new therapeutic options. The goal of our multiuniversity research team, composed of researchers from Stanford University, Brown University, the University of California at San Francisco (UCSF), and the University College London (UCL), is to substantially elevate the fundamental understanding of brain information processing and its relationship with sensation, behavior, and injury. Our team was assembled to provide expertise ranging from neuroscience to neuroengineering and to neurological and psychiatric clinical guidance, all of which are critical to the overarching research goal. By employing a suite of innovative experimental, computational, and theoretical approaches, the Defense Advanced Research Projects Agency (DARPA) Reorganization and Plasticity to Accelerate Injury Recovery (REPAIR) team has set its sights on learning how the brain and its microcircuitry react (e.g., to sudden physiological changes) and what can be done to encourage recovery from such (reversible) injury. In this article, we summarize some of the team's technical goals, approaches, and early illustrative results.

The precise brain state on a millisecond time scale can predict specific fluctuations in arm movements.

Methodology: Bridging Experiment and Brain Models

The ultimate goal is to understand how the information in the distributed neural circuits of the brain reorganizes and plastically adapts to laboratory disruptions designed to reversibly mimic brain injury. Our approach involves a new generation of data-driven mathematical models of brain circuits and their connection with complex behavioral tasks in primates that are enabled with a suite of novel experimental tools (see Figure 1). In the following, we illustrate a few of these methods, which include projecting input directly onto specifically targeted brain microcircuits and thus writing in neuromodulatory signals. These methods also enable the simultaneous read out and write in of real-time neural responses across multiple spatial and temporal scales of network activity.

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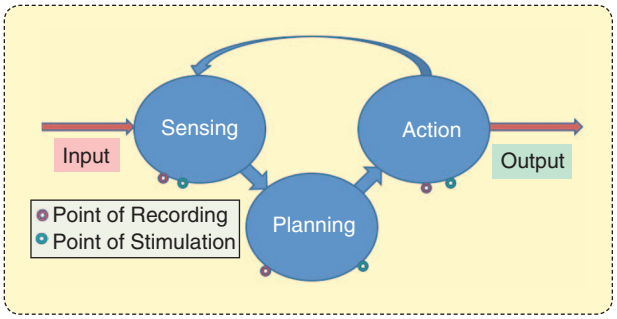

FIGURE 1 A schematic representation of the project approach. Multiple sites in the cortex are subject to simultaneous optical stimulation and electrophysiological recording, accompanied by behavioral observations to acquire experimental input for mathematical models of the brain states.

A central theme in the experimental methodology of our team is the combination of recently developed (and developing) molecular biology tools for enabling light sensitization of specific classes of neural cells and their projections (optogenetics) together with microscale devices that provide spatially targeted means of light delivery and electrical measurement. Ultimately, we hope that, with the advanced analytical methods for interpreting the recorded electrical signals from populations of neurons in real time, the readout and write-in operations can be combined in a closed-loop implantable system for the purpose of dynamical adjustment of errant brain states. This is an example of where the required team synergy among experiment, computation, and theory is imperative. Any such future closed-loop system will work as efficiently, and be as meaningful, as the level of understanding of the brain reorganization that we aim to achieve via the data-driven mathematical models.

Light can be used to dramatically increase or decrease the number of action potentials emitted by neurons in the cerebral cortex.

Experimental Tools: Optogenetics and Microarray Cortical Implant Devices

The ability to modulate populations of specific neurons on the biologically relevant time scale of milliseconds is essential for advancing our fundamental understanding of neural function and dysfunction. Modulating neural circuits by electrical stimulation (injecting current into brain tissue) is a well-established tool in electrophysiology and clinical neurosurgery, even if many uncertainties are inherently present given such

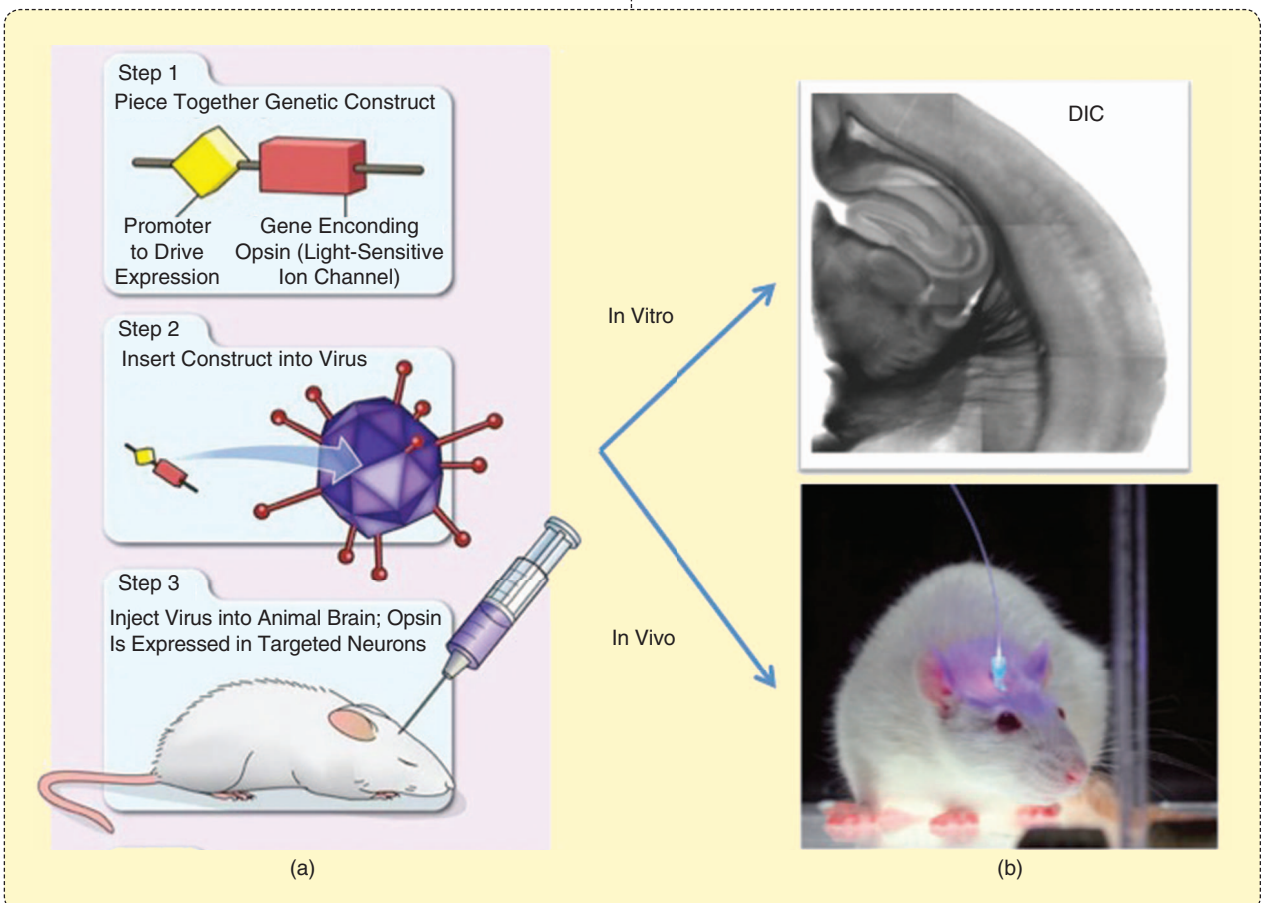

FIGURE 2 Basic principles of optogenetic transduction of selected neural circuits: (a) a schematic of the molecular biology steps in preparing target opsin proteins (Steps 1 and 2) before local injection into the brain of the genetic constructs enveloped in a viral capsid (Step 3) (adapted from [8]) and (b) example of how research utilizes in vitro brain slices with specific isolated circuits and in vivo animal studies with embeded optoelectronic devices for targeted optical neuromodulation.

nonspecific activation of cells by the complex flow of current pathways [1]. A new approach to neural stimulation began with the discoveries of the light-sensitive ion channel, Channelrhodopsin-2 (ChR2) [2], and the optically activated chloride pump, halorhodopsin (NpHR) [3]. By combining genetic and optical methods, these discoveries were rapidly advanced by our team coinvestigator to create a fundamentally new method (optogenetics) to target neurons [4] (see Figures 2 and 3).

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Light-induced modulation via optogenetics offers a targeted means for neural cell excitation and inhibition as well as well-defined control of neuronal events with millisecond time resolution [5]. Among practical advantages over electrical stimulation, the use of optical stimulation is the minimal interference with simultaneously recorded electrophysiological signals. Under the DARPA REPAIR project, the Stanford team component includes advancing the underlying molecular biology by the application of molecular trafficking principles for the development of new generations of optogenetic constructs [6], in conjunction with new optoelectronic devices and translation to nonhuman primates [7], [8].

The recent developments in applying these subcellular and transcellular trafficking strategies now extend optogenetic control across most of the visible spectrum, while exhibiting increased potency of optical neural inhibition without increased light power requirement [6]. More broadly, this is paving the way to generalizable strategies for targeting cells based not only on their genetic identity but also on patterns of neuronal projections. New optogenetic approaches in nonhuman primates and rodents (as a crucial cross-species test bed) will be employed to modulate and selectively shut down brain areas of choice to emulate (reversibly) particular types of brain injury and to guide our models to address and enable brain recovery from injury [9].

As a second key neurotechnology element, the team is also codeveloping microscale implantable micro/optoelectronic devices to engage neural signals across multiple brain microcircuits at a single neuron resolution. These devices focus on integrated, monolithic optrode arrays that enable patterned and targeted spatio-temporal optical projection of neural stimuli while electrophysiologically recording from the affected neurons for characterizing their neuromodulated network response [10]. The implantable dual-function chronically implanted devices, in turn, are interfaced to integrated optoelectronic devices and on-board telemetry. For targeted light delivery in brain tissue, optical fibers have already seen a wide use in optogenetics to date, given their abundant commercial availability as flexible (if fragile), low-loss optical waveguides. An optical fiber also allows in vivo fluorescence detection in the intact brain for minimally invasive assessment of opsin expression and its spatial location while a dual-function modulate/probe device is being inserted in a given experiment [7]. In Figure 4, we illustrate one integrated dual-function single and multielement optoelectronic devices developed at Brown where an optical fiber is integrated into an intracortical microelectrode array (MEA). These first-generation devices have been chronically implanted in rats to enable their use in behaviorally trained freely moving animals for up to six months [11]. In doing so, the device has enabled us to elicit neuromodulation while simultaneously mapping single-unit electrophysiological response from neuronal populations in ChR2-expressing rats in vivo as a device test bed. While leaving the interpretation of the underlying neuroscience elsewhere, the data are shown here to demonstrate the utility of the device, a chronic implant, scalable to primate use.

As a final example of experimental tools, we have recently translated several optogenetic constructs from rodents to nonhuman primates [7], [8]. As shown in Figure 5, light can be used to dramatically increase (ChR2) or decrease (eNpHR2.0) the number of action potentials emitted by neurons in the cerebral cortex. These early experiments highlighted the need for further development of a coaxial optrode, so as to minimize the impact on tissue, which is now underway.

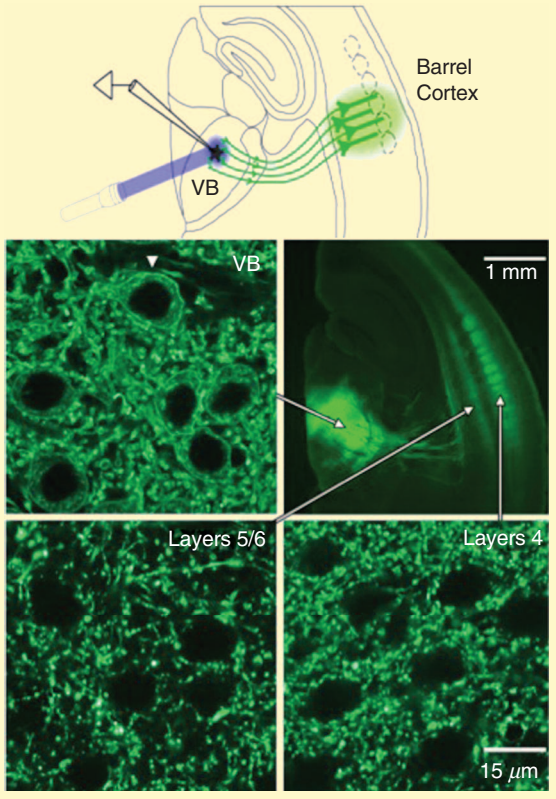

FIGURE 3 An example of opsin transduction of specific thalamocortical pathway in a mouse brain slice. The images employ fluorescent protein as the marker for Channelrhodopsin expression, viewed under different magnifications. Here the virus was injected into the ventrobasal thalamus and projected expression through axonal pathways to the thalamic arbors in the cortex but did not express ChR2 in the cortical cells themselves [21].

Goal-directed movements rely on the integration of multiple sensory signals.

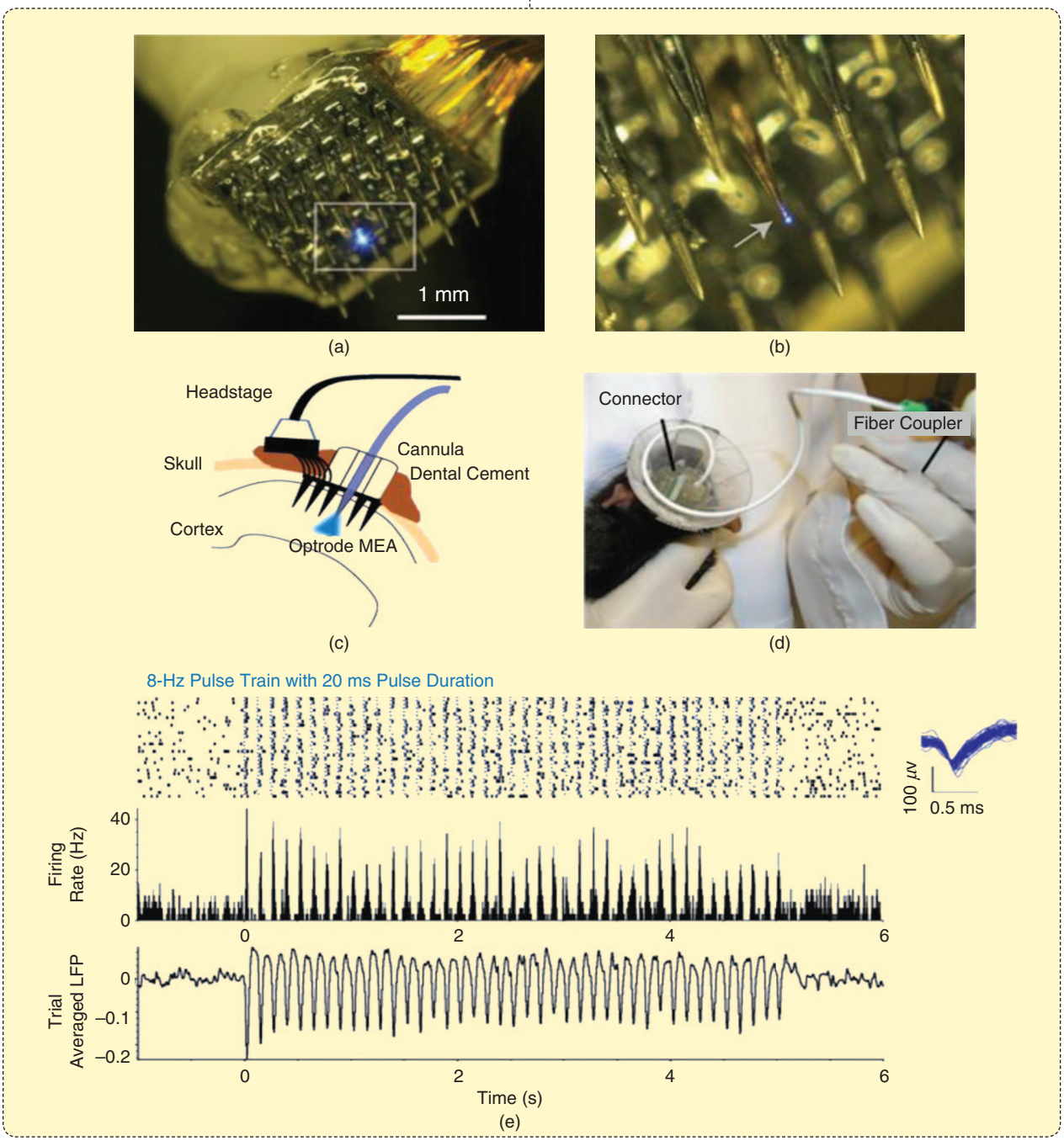

FIGURE 4 Optoelectronic microarrays: (a)–(d) the implementation of a rodent compatible, here a 6 × 6 intracortical multielectrode array, where one of the tapered shank electrodes has been replaced by a conformally identical optrode (tapered optical fiber) and (e) an experimental recording from one ChR2-transduced rat where the viral injection and subsequent placing of the optrode MEA targeted the posterior parietal cortex. Across the MEA, we could, in this instance, optically evoke a neural response from cells that were well synchronized in terms of their action potential (spike) firing rates as well as local field potentials modulation with the laser excitation. (Adapted from [11].)

Novel Behavioral Experiments to Inform Data-Driven Mathematical Models of the Brain

We are also developing a new generation of complex behavioral tasks, with nonhuman primates and rodents, whereby we will quantify brain performance over a much broader range of tasks and contexts (e.g., maze tasks, dexterity tasks, image recognition, and freely moving tasks [12]). Moreover, the UCSF effort includes measuring directly how animals use surrogate information delivered artificially, via electrical microstimulation and/or optogenetic stimulation. These new behavioral and neurophysiological experiments will provide a broad range of data to develop, test, and make subsequent experimental predictions using new mathematical models. The modeling effort at UCL and UCSF, spanning Stanford and Brown, includes hidden linear and nonlinear dynamical systems, Bayesian estimation, deep belief networks, and the associated statistical and machine-learning methods. One example employs a dynamical systems perspective to gain insight into how neural populations act in a coordinated fashion to converge on specific brain states [13] and how these brain states can serve as the initial state for a dynamical system that produces movement activity and arm movement [14]. Furthermore, explicit dynamical models of the population activity on a single trial reveal transitions between different dynamical laws that correlate well with behavioral events [15]; indeed, the precise brain state on a millisecond time scale can predict specific fluctuations in arm movements [16].

Another example involves understanding how the dynamics of neural populations can give rise to elements of sensorimotor behavior. Goal-directed movements, such as reaching, rely on the integration of multiple sensory signals, e.g., visual and somatosensory information about the arm and the world in which it moves. This process appears to be adaptive and statistically efficient [17]–[19], despite the fact that different signals are represented in the brain in different ways and are related by complex, nonlinear mappings. Understanding the dynamics of this process will be fundamental to designing techniques to write-in new behaviorally relevant information. We asked how the brain could learn de novo to integrate complex multidimensional signals. We show that integration can be achieved by extracting the underlying statistical properties of the combined signals, using density estimation via a restricted Boltzmann machine (RBM). We also depict that the trained RBM model integrates nearly optimally, i.e., it is able to learn on a broad class of representations, maintain statistical information about the representations, and generate missing data (e.g., make predictions about one modality based on another) [20].

Light-induced modulation via optogenetics offers a targeted means for neural cell excitation and inhibition as well as well-defined control of neuronal events with millisecond time resolution.

Summary and Outlook

There is a broad range of new neuroscience and neuroengineering research now underway. Entirely new classes of behavioral experiments, neurophysiological recordings and modulation, and essential analytical modeling and analysis techniques are emerging and being brought to help neurologically injured patients. New types of neural interface systems are now envisioned, ranging from those that

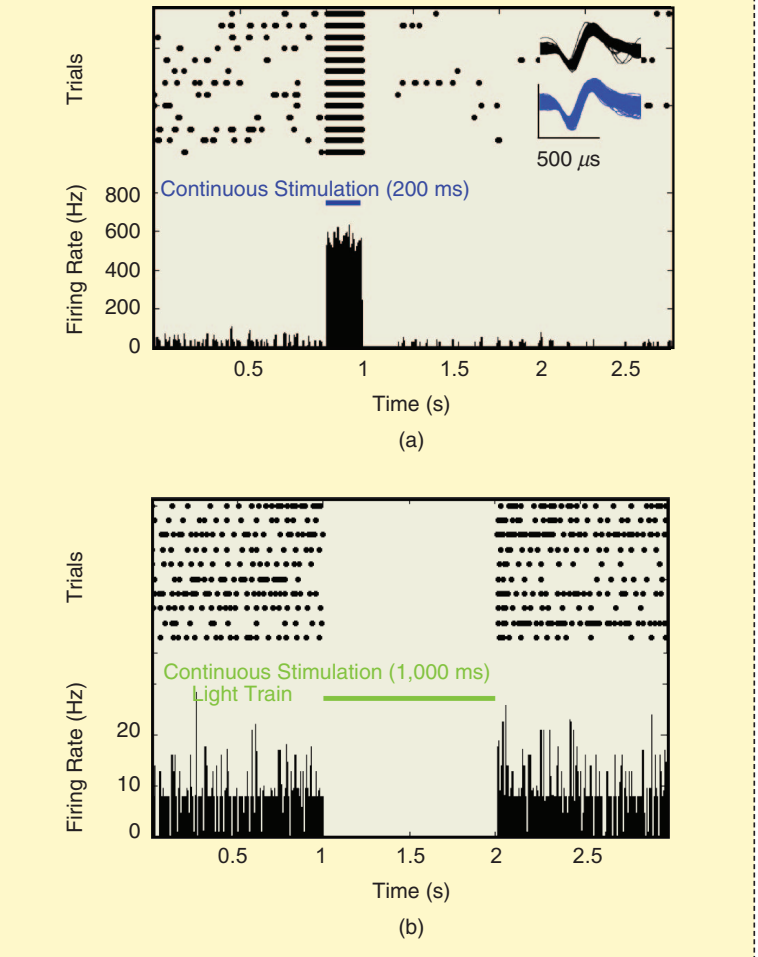

FIGURE 5 Optogenetic activation and inhibition in rhesus monkey cortical neurons: (a) a 200-ms blue-light pulse successfully excites a transfected neuron (AAV5-Thy1-ChR2-YFP) in motor cortex, as evident in spike trains recorded in 13 trials. Individual spike trains (upper panel) and histogram (lower panel) are shown; the action potential waveform is identical to when the neuron fires spontaneously (inset) and (b) a 1,000-ms green-light pulse suppresses a neuron transfected with a different construct (AAV5 Thy1-eNpHR2.0-YFP), as anticipated. (Modified from [7].)

can sense, compute, and interact directly with the nervous system to those that may shed new insights into neurological function and dysfunction, thereby enabling existing therapies to be retargeted and delivered more effectively. At the heart of this research enterprise is interdisciplinary and collaborative research teamwork, where together it is possible to more quickly and fully gain new knowledge and apply this understanding to those in need.

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