Optogenetics

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Abstract— **The brain is made up of an incredible number of different kinds of neuron, which vary in their shapes, molecular compositions, and connectivity patterns, as well as in how they change in different disease states. Understanding how these different kinds of neuron work together in brain circuits to implement perceptions, emotions, decisions, and actions, and how flaws in specific neuron types result in brain disorders, is an ongoing high priority for neuroscience. Over the last several years we have developed a rapidly-expanding suite of genetically-encoded reagents (e.g., ChR2, Halo, Arch, Mac, and others) that, when expressed in specific neuron types in the nervous system, enable their activities to be powerfully and precisely activated and silenced in response to pulses of light. These tools are in widespread use for analyzing the causal role of defined cell types in normal and pathological brain functions. We have begun to develop hardware to enable complex and distributed neural circuits to be precisely controlled, and for the network-wide impact of a neural control event to be measured using distributed electrodes and fMRI. We discuss our pre-clinical work on translation of such tools to support novel ultraprecise neuromodulation therapies for human patients.**

I. Introduction

The brain is made up of an incredible number of different kinds of neuron, which vary in their shapes, molecular compositions, and connectivity patterns, as well as in how they change in different disease states.

Ideally, one would be able to silence the activity of a specific kind of neuron, for a very precisely defined period of time, so as to reveal the neural computations, behaviors, or pathologies for which those neurons were necessary. And, ideally one would be able to activate a specific kind of neuron selectively, so as to reveal what neural activity patterns, behavioral functions, or pathological states those neurons were capable of initiating or sustaining.

Below we describe the suite of technologies we have developed to meet these needs, by enabling the electrical activity of specific neurons to be controlled precisely with light.

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II. Results

In 2005, we reported that expression of the algal light-gated cation channel channelrhodopsin-2 (ChR2), a membrane protein from *C. reinhardtii*, in neurons, enabled the neurons to fire electrical action potentials in response to brief pulses of blue light [1]. In 2007, we reported the use of the archaeal light-driven chloride pump halorhodopsin (Halo/NpHR) from *N. pharaonis* to hyperpolarize neurons in response to yellow light [2]. Three years later, we reported a second class of light-driven neural silencer, the light-driven outward proton pump, which could support extremely powerful neural silencing, an order of magnitude greater than that mediated by the original halorhodopsins, as exemplified by the molecule Arch from *H. sodomense* [3], which can result in ~100% shutdown of neural activity in the awake brain in response to green or yellow light. Other light-driven outward proton pumps, such as the molecule Mac from *L. maculans*, can be used to silence neurons in response to blue light [3].

These molecules require no chemical co-factors in the mammalian brain, and operate at high enough speeds to enable driving or deletion of individual action potentials. We have distributed these tools to approximately 400 groups around the world, where they are used in animals (either engineered to be transgenic, or expressing the genes in defined neurons after viral delivery), to study the roles that defined neurons play in normal and abnormal brain computations. We continue to search genomic resources for new tools [7], and to optimize existing tools through mutagenesis or appending of useful sequences (e.g., [3]).

Recently we have begun to develop optical hardware for driving and silencing defined 3-dimensional neural circuits in the brain, thus opening up the ability to analyze how different circuits work together in the brain to mediate computations [4]. We have also begun to develop strategies for measuring the circuit-wide impact of perturbing a given cell type using awake animal fMRI [5] and neural recording, thus enabling us to derive principles of how to optimally control a neural circuit, both for purposes of scientific understanding as well as for clarifying the principles underlying the discovery of new therapeutic targets (i.e., towards which drugs or electrical probes might be directed).

Finally, we have pursued pre-clinical studies of the potential use of these technologies, in non-human primates, thus providing preliminary support for a new generation of optical prosthetics for precision treatment of brain disorders [6]. Given the increasing use of implanted electrical stimulators to treat deafness, Parkinson's disease, and other

neurological conditions, as well as progress in human gene therapy using adeno-associated virus (AAV) [8], our early work on the safety and efficacy of opsin expression and function in the non-human primate brain suggests that new kinds of optical brain control therapy may be possible.

In summary, we have developed a suite of molecular and hardware tools that enable the activity of defined neurons embedded within brain circuits to be precisely controlled, opening up the ability to study their functions as well as to potentially control neurons that have gone awry in states of brain pathology.

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