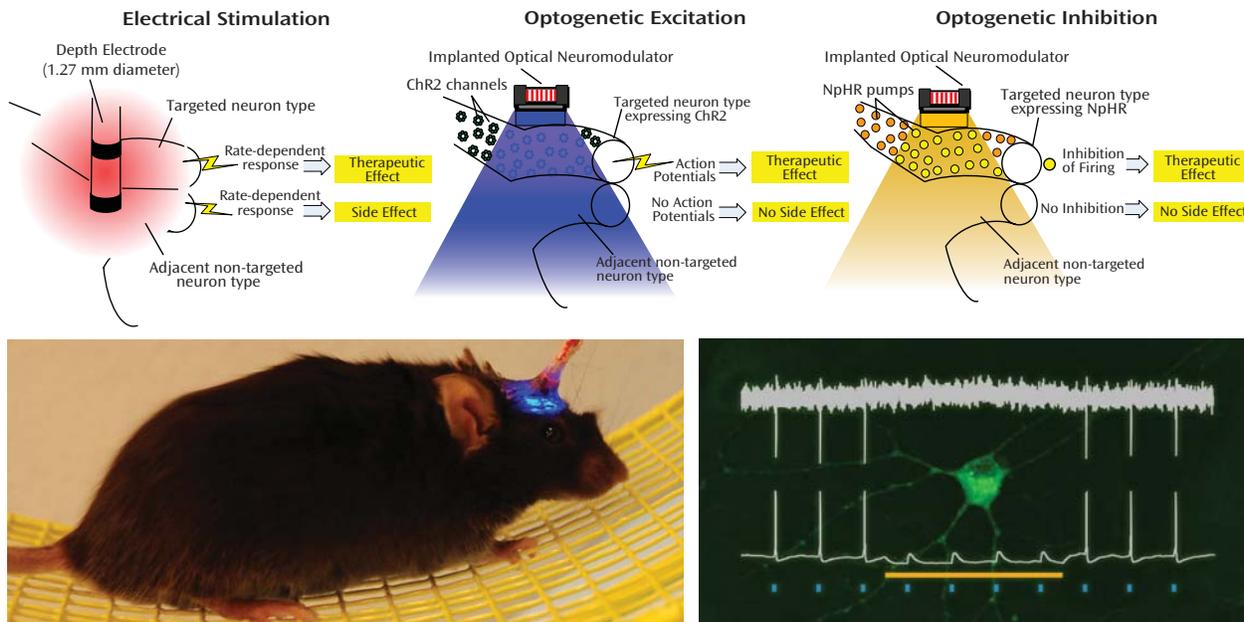


Controlling Neuronal Activity



Top: Electrical versus optogenetic neuromodulation; the electrode non-specifically affects all nearby neurons (left), whereas blue or yellow light emitting devices affect only the neurons containing excitatory ChR2 protein (center) or inhibitory NpHR protein (right). (Figure adapted/modified with permission from A.M. Aravanis et al., “An Optical Neural Interface: In Vivo Control of Rodent Motor Cortex With Integrated Fiberoptic and Optogenetic Technology” [J Neural Eng 2007; 4:S143–S156]. Copyright © J Neural Eng. Bottom left: A prototype implantable light-delivery device based on diode technologies can be directly mounted onto laboratory animals used as disease models (Image courtesy of the Deisseroth Lab). The use of yet more compact emitters may smooth the path to preclinical or clinical use. Bottom right: neurons expressing ChR2 and NpHR can be optically silenced or driven to fire precisely-patterned action potentials (Figure adapted/modified with permission from F. Zhang et al., “Multimodal Fast Optical Interrogation of Neural Circuitry” [Nature 2007; 446:633–639]. Copyright © Nature.

With a new technology called optogenetics, it is possible to turn neuronal activity on and off in distinct neuronal populations, using cell-type specific, optically-sensitive, molecular, neuronal activity “switches.” These “switches” are microbial, light-sensitive ion conductance-regulating proteins, exemplified by channelrhodopsin-2 (ChR2) and halorhodopsin (NpHR). They are individually introduced into neuronal populations in the brain and become part of the cellular machinery. Ion flux-regulating activity of these “switches” can be controlled externally with light pulses. ChR2 is a cation channel that allows sodium ions to pass into a neuron after it has been activated by approximately 470 nm blue light (thereby increasing activity of the neuron and increasing action potentials). NpHR is a chloride pump that transfers chloride anions into the neuron after it has been activated by approximately 580 nm yellow light (thereby increasing accumulation of negative charge inside the cell and suppressing activity of the neuron). For application of this technology, light of the proper wavelength is delivered to the brain region of interest using a fiberoptic-based system or a light-emitting diode (LED). ChR2 and NpHR can be controlled independently to either increase action-potential firing of specific target neurons or to suppress neural activity, respectively, in intact tissue. In animal experiments, the LED or fiberoptic can be tethered to an external power source with lightweight flexible connectors, allowing stimulation during normal, freely moving behavior. The genes encod-

ing these proteins are introduced into the brain with viral vectors and are expressed in distinct populations of neurons in vivo using specific DNA promoters fused to the gene, thereby guiding expression only in the cell type of choice.

Currently, these molecular “switches” are being used to interrogate the functions of specific cell populations within complex neural circuits of living animals in order to better understand the contribution of defined cell types to behavior. For example, dopamine-releasing neurons are being targeted by this approach, with the goal of understanding the causal role of specific patterns of activity of these cells in behaviors relating to reward and depression. Preclinical work of this kind will help us better understand the circuits involved in human disease. In the long run, clinical studies may eventually allow—for example—the use of NpHR or ChR2 protein to be introduced into human cell types in diseases for which candidate targets of surgical intervention are already known, i.e., the subthalamic nucleus in Parkinson’s disease, the hippocampal seizure foci in epilepsy, and the subgenual cingulate in depression.

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