**Optogenetics Annotated Bibliography**

Peer Reviewed Journal Sources

[1] Fenno L, Yizhar O, Deisseroth K. **“The development and application of optogenetics.”** *Annu Rev Neurosci*. 2011;34:389-412. doi: 10.1146/annurev-neuro-061010-113817.

This review paper comes from the same lab that published the first study introducing optogenetics in 2005. It gives a brief but useful background of the utilization of opsin, and it summarizes the major types of light-sensitive channels developed from both type I and type II opsins between 2005 and 2011. The authors also compared the mutation sites, deactivation time constant, and activation wavelength of different modified opsins. While only one inhibitory channel (eNpHR) is mentioned in this review paper, other channels (eBR, iC1C2) are generated and are more commonly used today. The application of optogenetic tools in different animal models are also briefly described.

[2] Kim CK, Adhikari A, Deisseroth K. **“Integration of optogenetics with complementary methodologies in systems neuroscience.”** *Nat Rev Neurosci.* 2017 Mar 17;18(4):222-235. doi: 10.1038/nrn.2017.15.

Since 2005, the development of optogenetics enabled the rapid growth of neuroscience research and, as a result, greatly broadened our understanding of neural circuits and behaviors. This more recent review focuses on the utilization of optogenetic tools. It summarizes several approaches to achieve cell-type specific and circuit-specific targeting, and then gives examples of integrating optogenetics with variety of in vivo electrophysiology, calcium imaging, as well as neuroanatomy studies.

[3] Zhang H, Cohen AE. **“Optogenetic Approaches to Drug Discovery in Neuroscience and Beyond.”** *Trends Biotechnol.* 2017 Jul;35(7):625-639. doi: 10.1016/j.tibtech.2017.04.002.

This review focuses on the utilization of optogenetics on drug discovery. Optogenetics offers several key advantages over traditional drug discovery cell-based assays, mainly due to its ability to deliver temporally and spatially precise stimuli to elicit defined patterns of molecular and cellular activity. This paper summarized the use of optogenetics in high-throughput screening, phenotype screening, and drug toxicology studies. The author suggested that with further integration and modification, optogenetics should be able to lead low-cost drug screening approaches.

[4] Galvan A, Stauffer WR, Acker L, El-Shamayleh Y, Inoue KI, Ohayon S, Schmid MC.

**“Nonhuman Primate Optogenetics: Recent Advances and Future Directions.”** *J Neurosci.* 2017 Nov 8;37(45):10894-10903. doi: 10.1523/JNEUROSCI.1839-17.2017.

Although mainly used in non-primate animal model studies, optogenetics have great potential in studying complex behaviors and circuits in nonhuman primates. Since the first published nonhuman primate optogenetic study published in 2009, the techniques have been modified and are further adapted to be used in nonhuman primates. This review paper describes several breakthroughs in nonhuman primate optogenetic studies which provides foundation for future circuit-based therapy.

[5] Boyden ES, Zhang F, Bamberg E, Nagel G, Deisseroth K. **“Millisecond-timescale, genetically targeted optical control of neural activity.”** *Nat Neurosci*. 2005 Sep;8(9):1263-8. doi: <https://doi.org/10.1038/nn1525>

The authors first introduced the technique of using virus-mediated expression of channelrhodopsins (ChR) in cultured hippocampal neurons and eliciting excitation of ChR2-expressing neurons with blue light pulses. They studied the properties of neuron spiking under different light-pulse duration and frequency, as well as the post-synaptic response to light-induced pre-synaptic excitation. They have also shown that heterogeneous populations of neurons can be controlled in concert, thus it’s possible to stimulate a group of neurons simultaneously in vivo for future studies.

[6] Volkov O, Kovalev K, Polovinkin V, Borshchevskiy V, Bamann C, Astashkin R, Marin E, Popov A, Balandin T, Willbold D, Büldt G, Bamberg E, Gordeliy V. **“Structural insights into ion conduction by channelrhodopsin 2.”** *Science.* 2017 Nov 24;358(6366). doi: 10.1126/science.aan8862.

Channelrhodopsins (ChRs) is the most frequently used tool in optogenetics. This paper first determined the high-resolution structure and structural mechanisms of ChR2 and its C128T slow mutant, including their ion conduction pathway (which comprised four cavities that are separated by three gates) and hydrogen bonds (which is thought to be important for gating). Knowing the structure of ChR will greatly facilitate the understanding of its functioning, the mechanisms of channel opening and closing, and eventually benefit the development of optogenetic tools.

[7] Wright KN, Dossat AM, Strong CE, Sailer LL, Pavlock SM, Kabbaj M. **“Optogenetic inhibition of medial prefrontal cortex projections to the nucleus accumbens core and methyl supplementation via L-Methionine attenuates cocaine-primed reinstatement.”** *Integr Zool.* 2018 Oct 15. doi: 10.1111/1749-4877.12365.

Optogenetics have the advantage of targeting a specific circuit and manipulating the neural activity within that circuit. This study utilized this advantage and manipulated mPFC-NAc pathway by injecting a NpHR-expressing AAV into mPFC and implanting optic fiber onto NAc. They inhibit the mPFC-NAc pathway with light pulses and they found that specifically inhibiting the mPFC-NAc projection could attenuate cocaine-primed reinstatement, mimicking the effect of L-Methionine.

[8] Bernal Sierra YA, Rost BR, Pofahl M, Fernandes AM, Kopton RA, Moser S, Holtkamp D, Masala N, Beed P, Tukker JJ, Oldani S, Bönigk W, Kohl P, Baier H, Schneider-Warme F, Hegemann P, Beck H, Seifert R, Schmitz D. **“Potassium channel-based optogenetic silencing.”** *Nat Commun*. 2018 Nov 5;9(1):4611. doi: 10.1038/s41467-018-07038-8.

The application of current optogenetic inhibitors (inward-directed Cl- pumps, outward-directed proton/Na pumps) raises problems due to changes in ion distributions. Since K+ has equilibrium potential near resting potential of excitable cells, activation of K channels can generate strong inhibition without major changes in transmembrane ion gradients. Therefore, a light-activated K channel could be a better option for optogenetic inhibition. This study established a two-component optical silencer system by using photo-actives adenylyl cyclases (PACs) and small cyclic nucleotide-gated K channel (SthK). They’ve shown in this study that brief pulses of blue light lead to reversible inhibition of neuron firing.

[9] Shang C, Chen Z, Liu A, Li Y, Zhang J, Qu B, Yan F, Zhang Y, Liu W, Liu Z, Guo X, Li D, Wang Y, Cao P. **“Divergent midbrain circuits orchestrate escape and freezing responses to looming stimuli in mice.”** *Nat Commun.* 2018 Mar 26;9(1):1232. doi: 10.1038/s41467-018-03580-7.

Looming visual stimuli elicit defensive behaviors such as escape and freezing in mice. This study not only utilizes optogenetic tools to map cell-type specific circuits underlying defensive behaviors, but also integrates optogenetics with slice electrophysiology and calcium imaging to study how these neural circuits participate in escape or freeze behaviors. They found that two distinct groups of PV+ neurons in superior colliculus formed divergent visual pathways to the PBGN and LPTN, respectively. Selective activation of the PV+ SC-PBGN and PV+ SC-LPTN pathways in mice mimicked the defensive behaviors.

[10] Vander Weele CM, Siciliano CA, Matthews GA, Namburi P, Izadmehr EM, Espinel IC, Nieh EH, Schut EHS, Padilla-Coreano N, Burgos-Robles A, Chang CJ, Kimchi EY, Beyeler A, Wichmann R, Wildes CP, Tye KM. **“Dopamine enhances signal-to-noise ratio in cortical-brainstem encoding of aversive stimuli.”** *Nature.* 2018 Nov;563(7731):397-401. doi: 10.1038/s41586-018-0682-1.

VTA dopamine neurons release dopamine to medial prefrontal cortex (mPFC), potentially participate in mPFC–dPAG neurons mediated respond to aversive stimuli. This study manipulates and record circuits activity by combining optogenetics with calcium imaging. They identified that mPFC–dPAG neurons increase firing as a response for aversive stimuli. In consistent, light-activation of mPFC–dPAG projection promote aversion. Additionally, they have shown that light activation of dopaminergic projection in mPFC enhances mPFC–dPAG mediated aversion.

Website Sources

[1] <https://www.youtube.com/watch?v=QA67v4vSg00>

An educational video explaining the origin of opsins, the principle of light-induced neural activity changes, and the potential application of optogenetics in human brain disorders.

[2] <https://www.ibiology.org/neuroscience/optogenetics/>

A talk by Dr. Karl Deisseroth explaining their journey of developing optogenetic tools, the process of modifying this tool, and applying it to freely moving animal models to study behavior and circuits.

[3] <https://www.jove.com/video/50291/a-method-for-high-fidelity-optogenetic-control-individual-pyramidal>

A tutorial video from JOVE showing the complete procedure of viral injection of opsin-expressing virus into rat brain, followed by fiber implantation, light delivery, and in vivo recording of ChR/NpHR-expressing cells.

[4] <https://www.jove.com/video/50004/fiber-optic-implantation-for-chronic-optogenetic-stimulation-brain>

This JOVE video is showing the implantation of optic fiber for chronic optogenetic stimulation to mice brain.

[5] <http://web.stanford.edu/group/dlab/optogenetics/sequence_info.html>

This is a useful website built by Deisseroth lab, it contains resources for up-to-date optogenetic tools including viruses, protocols, information regarding hardware setup, and instructions for requesting plasmid/virus.

[6] <https://www.med.unc.edu/genetherapy/vectorcore/in-stock-aav-vectors/>

The UNC Vector core is a good core facility that stock premade AAV vectors designed and used by Dr. Karl Deisseroth (Stanford University), Dr. Ed Boyden (MIT), Dr. Ian Wichersham (MIT), Dr. Naoshige Uchida (Harvard University) and Dr. Nirao Shah (University of California at San Francisco). You can select and order specific stereotypes of AAV with the plasmid you need for optogenetic research, or have vector custom made by this core.

[7] <https://www.jax.org/research-and-faculty/resources/optogenetics-resource>

This is the website for The Jackson Laboratory Repository where you can order transgenetic mouse lines expressing proteins that activate, inhibit or detect neuronal activity, as well as cre-expressing strains and strains expressing optogenetic effector proteins in a Cre-dependent manner.

[8] <https://www.addgene.org/optogenetics/guide/>

An informational website with a comprehensive introduction about optogenetics and a summary of channels with distinct properties. It also has a step to step guide for designing a optogenetic experiment, from opsin delivery system to choosing color of light for activation.

[9] <https://www.youtube.com/watch?v=6WgdWsm_FVs>

An experiment video illustrating an application of optogenetics in C. elegans. This experiment was conducted by Karl Deisseroth’s lab at Stanford University-

[10] <https://neuronline.sfn.org/Articles/OTS/Next-Generation-Optogenetics-Tools-and-Applications-Agenda>

The topic for Society for Neuroscience Virtual Conference on September 20th, 2018 was “Next Generation Optogenetics: Tools and Applications”. They invited Ed Boyden and Karl Deisseroth, co-inventor of optogenetics, along with other leading investigators in the optogenetic field to give talks from the newest progress on light-control channels development to clinical application of optogenetics.