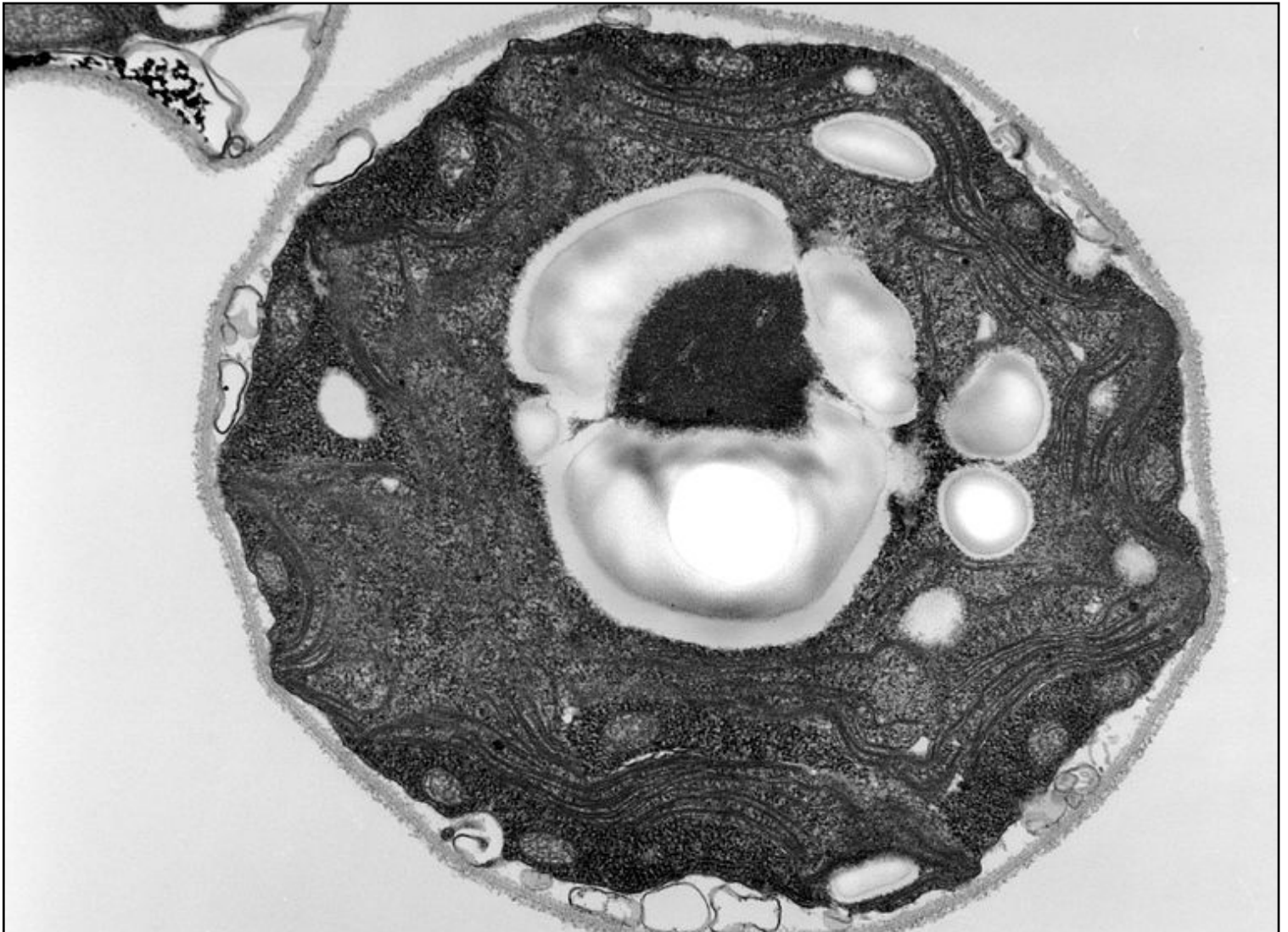


OPTOGENETICS

BY GEORGE PLUMMER



In the late 90s classic, *Men in Black*, Agents J and K, in their efforts to prevent earthlings from discovering the aliens that live amongst them, blind bewildered witnesses of alien activity with “neuralyzers,” to erase any immediate memories of extraterrestrials—effectively controlling their minds with a flash of light. In recent years, this science fiction has somewhat become a reality with the advent of optogenetics. This rising experimental method uses light-sensitive ion channels, genetically expressed in specific cells, to modulate neural activity with light. With a flash

Figure 1: Short exposures to light induce action potentials in neurons expressing channelrhodopsin, a main player in optogenetics. *Photo courtesy of Wikimedia Commons.*

of light at a specific wavelength, these channels open, modulating the ion concentrations of the cell, inducing or preventing activity.

Optogenetics comes out of a necessity in neuroscience to effectively control neural activity—the more specific, the better. Over thirty years ago, Francis Crick, the discoverer of DNA, with a new eye on neuroscience, described the need to develop methods to better con-

trol neurons to fully answer questions of the mind (1). To truly understand how the jumbled interconnected mush of the neurons called the brain conjures up thoughts, emotions, individuality, or even a basic motor output, the causal relationship of a neuron’s activity on the behavior of other neurons—or the entire organism—must be determined.

Inspired by these questions, several groups of scientists came to the idea

of using light for this goal of neural control. One group, lead by Gero Miesenbock, created the first brain with neurons controlled by light (2). Karl Deisseroth has since followed up with studies building on these ideas of creating neurons and expressing ion-channels that open after exposure to light, originally discovered by Georg Nagel and Peter Hegemann (3, 4). Thanks to their efforts, using light to control neurons has grown to become an integral tool in neuroscience. With these newfound abilities, what does this advance mean to neuroscience, and for the scientific community in general?

For neuroscience, this advance means a new level of specificity when controlling neurons. Methods of neural control and recording have existed in the past through electrical probes; however, these tools lacked precision

and finesse, and at the same time cast a small net, only activating or recording near the electrode. The genetic selectivity of controlled cells now allows the activation of fewer cells, or a greater population of select cell types, rather than whatever neurons that are near or touching the probe (5). Current techniques still require a level of intrusiveness, especially in mammals; however, with extremely small and translucent organisms, such as the zebrafish, scientists can control neurons with no invasive procedure (6, 7).

The idea of using light to control neural activity sounds exciting, even for people unfamiliar with neuroscience, and this excitement has been backed up. Deisseroth, champion and popularizer of optogenetics, and his team have uncovered parts of Parkinsonian and dopaminergic neural circuitry (8,

9). Adamantidis et al. have found neural substrates of sleep/awake states (10). Neural circuitry of escape responses in zebrafish and fruitflies have also been probed (11, 12). Rats and worms can also now be remotely controlled with light (13, 14). Optogenetic control of interneurons, which are interlaced amongst populations of various other cell types, has helped probe difficult and mysterious questions of brain waves (15). Optogenetics have also been able to manipulate visual behavior of monkeys (16). The utilization of light no doubt has opened doors for the ability to ask new questions.

Despite the achievements, this technique is still far from perfect. A recent publication presented the observation of how long-term expression of light-activated ion channels have altered axonal morphology and targeting (17). Critics

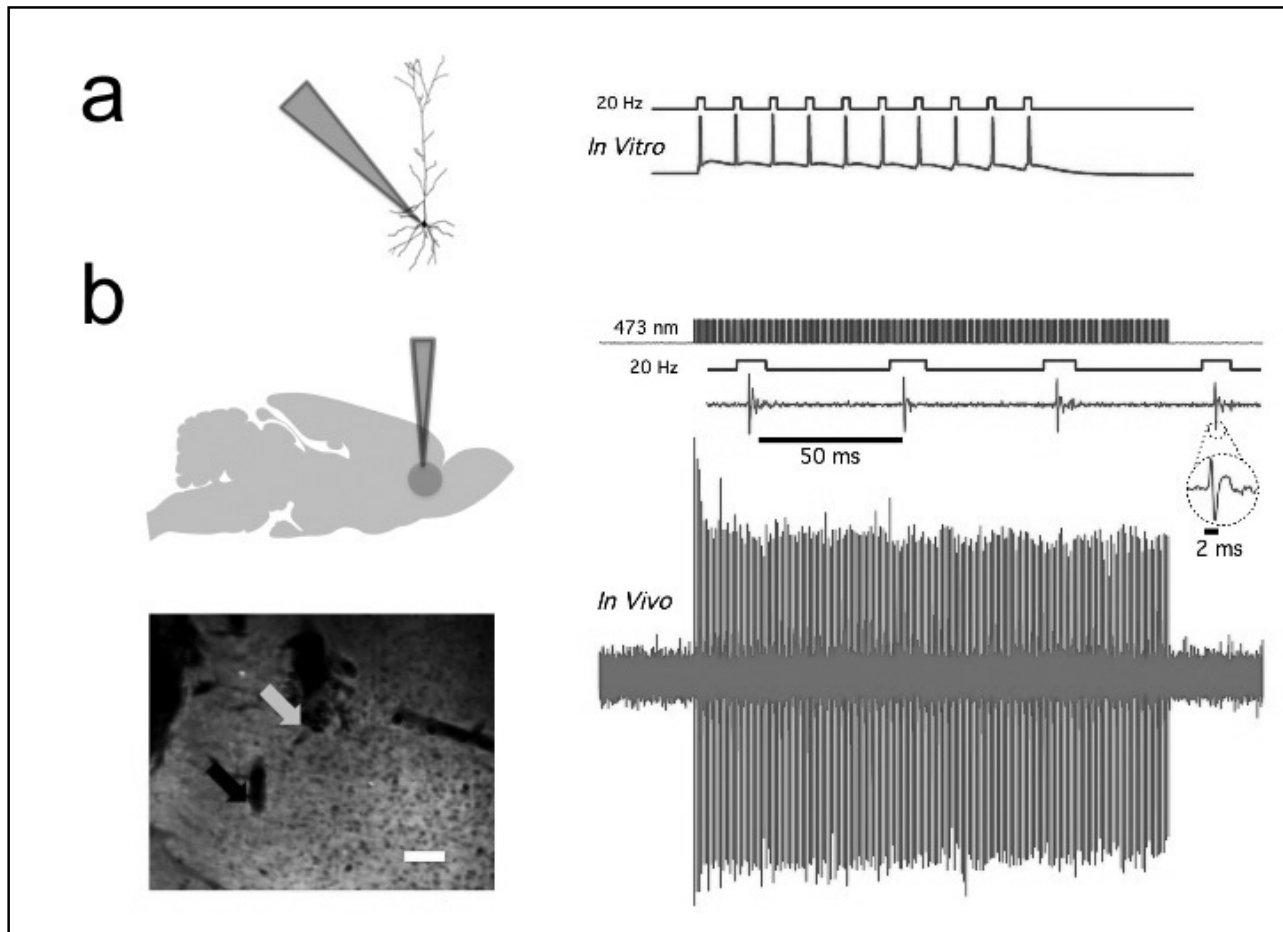


Figure 2: The ability to modulate neural activity is due to research conducted on this little green algae, *Chlamydomonas reinhardtii*, by Nagel and Hegemann. **Photo courtesy of Wikimedia Commons.**

have noted that although this method is thought to be more natural, the changes in ion concentrations far from perfectly mimic the real action potentials (18). The original discoverers Nagel and Hegemann associate small pores with the poor conductance, or the ability to allow ions through the channel, as the current limitation (19). Channels are also not entirely selective to ions, and thus can have slightly different effects from action potentials. Although following principles from the biophysical changes during neural activation and inhibition, these channels still are poor imitations of changes in neural activity. Even with these limitations, optogenetic approaches achieve what they set out for: activation and suppression of neurons. With more advances, optogenetics can overcome many of these deficits, but even as is, optogenetics can still answer many questions.

These advances have greater implications beyond neuroscience. For the scientific community, these advances reveal the importance of basic science research. The trajectory of optogenetics would not be possible without the research conducted on light sensitive algae by Nagel and Hegemann. In their research, they did not originally intend on discovering a way to use light to control cells - they were merely studying light sensitive bacteria.

Thanks to this discovery, Deisseroth and his colleagues were able to construct a new set-up, expressing these light sensitive ion channels in neurons, inducing activity. After the success of modulating neural activity with light, other ions channels were sought after, leading to light-sensitive ion channels to suppress neural activity. These discoveries have inspired the light-dependent control of other forms of neural modulation. Recent discussion has suggested the possibility of modulating GPCR dependent neural changes via light (20). Modulating cell activity with light has also been applied to studying cardiac function (21). Without

the initial understanding of these light sensitive channels, the knowledge of these molecules would not have been available for Deisseroth and others take advantage of. And without Deisseroth's novel use, others would not have been inspired to ask new, previously unanswerable questions or inspired similar uses of light for other optically controlled proteins.

While optogenetics has received publicity and acclaim, fundamentally, it is a technique, a tool. And with all tools, the significance comes down to how this tool will be used. The question now is, how will this new development be used, and for what questions?

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