Cracking the Retinal Code

Silicon "eyes" to help people with deteriorating vision are around the corner

BY CHRISTOF KOCH

CHRISTOF KOCH (*Koch*); GETTY IMAGES (*eye*)

Blindness is a private matter between a person and the eyes with which he or she was born.

THE SENTIMENT expressed by the late Portuguese writer José Saramago in his famous novel *Blindness* may be appropriate for a person born unable to see. But what about the tens of millions of people worldwide who suffer from a variety of degenerative diseases that progressively rob them of their eyesight? The problem arises in the nerve cells that line the back of their eyes, their retinas. Fortunately, help is on the way to restore some of the lost vision using advanced neuroengineering.

The hallmark of the two most common forms of adult-onset blindness in the West, age-related macular degeneration and retinitis pigmentosa, is that the photoreceptors responsible for converting the incoming rays of light into nervous energy gradually die off. Yet the roughly one million ganglion cells, whose output wires bundle up and leave the eyeball in the form of the optic nerve, remain intact. So visionary (pun intended) clinical ophthalmologists have paired up with technologists to bypass the defective parts of the retina by directly stimulating ganglion cells via advanced electronics. One of the most successful of such prosthetic devices, manufactured by a California company called Second Sight, uses a camera integrated into eyeglasses to convert images into electronic patterns. These patterns are sent to a small, 10- by 6-pixel microelectrode array surgically positioned onto the retina. It stimulates neural processes that relay their information in the form of binary electrical pulses, so-called action potentials or spikes, to the brain proper.

Spikes are the universal idiom in which neurons communicate with one another. Once we understand their whispering language, the neural code, we will be much closer to deciphering the ancient mind-body riddle. The sparse information relayed by this prosthetic—using 60 rather than the millions of photoreceptor channels—nonetheless helps. A recent interim report on a clinical trial with 30 patients who have end-stage retinal degeneration and who carry a Second Sight visual prosthetic concluded that the devices were safe and efficient. That is, they unambiguously improved visual acuity. Whereas untreated subjects could only tell light from dark, those with the prosthetic could detect hand movements and some could even count fingers. Although their measured acuity (20/1,260 compared with 20/20 for perfect vision) still leaves them legally blind, they do see something.

It is widely assumed that these residual visual abilities will improve as finer electrode arrays with a larger number of stimulation sites become available. Given the relentless progress in integrated circuit technology, this enhancement will undoubtedly happen. Yet others argue that what is really needed are more sophisticated encoding strategies. Think about it: What would happen to your computer if you were to suddenly turn all the transistors in its central processing unit simultaneously on and off? Clearly, the more you know about how software instructions are turned into patterns of electrical charge on transistor gates, the more productively you could manipulate the computer, hacking its transistors.

Exploiting the Neural Code

Sheila Nirenberg, a neuroscience professor at the Weill Medical College of Cornell University in New York City, and her Ph.D. student Chethan Pandarinath have just demonstrated this enhanced understanding of neural code by using the latest techno craze, optogenetics [see "Playing the Body Electric," by Christof Koch; Scientific American Mind, March/April 2010]. This method targets specific groups of nerve cells in mice that have been infected with genetically modified viruses that express a protein called channelrhodopsin-2 (ChR2). The viruses cause the neurons to express ChR2 in their surface membrane; ChR2 is a light-sensitive protein that responds to blue light. Shoot a pulse of blue light at a cell that expresses it, and it will respond with an electric signal that, if large enough, leads to an action potential, or spike. Any group of neurons can be made to fire on

command provided that they carry the molecular signature targeted by the virus. Nerve cells that do not have the appropriate molecular signature will not express ChR2. Optogenetics is hot because it allows researchers to deliberately intercede at any point within the tightly woven networks of the brain, moving from observation to manipulation, from correlation to causation.

To appreciate the beauty and specificity of Nirenberg's approach, it is important to realize that there is not just a single homogeneous group of retinal ganglion cells leaving the eye. Rather about 20 distinct types of cells exist, each one specialized for a different task. Some ganglion cells respond only to the onset of light but not when it ceases ("on" cells), whereas a second set signals the reverse—they respond with spikes when light is turned off ("off" cells) but are silent when they see a bright region. If a microelectrode array could simultaneously stimulate both on and off cells—as would happen with an all-electronic strategy—it would confuse the visual brain because it would appear that light had just been turned both on and off simultaneously! Other populations of ganglion cells carry information relating to a specific wavelength (involved in color vision), whereas still others convey information about things moving downward or sideways, and so on. In a sense, all of us have 20 different views of the world, emphasizing varying aspects of the visual environment. How these fractionated and disparate views are unified to yield the coherent picture of the world that we perceive consciously remains deeply puzzling.

Fortuitously, it looks as if each of these cell types has its own distinct molecular bar code. This knowledge can be used to restrict the expression of the optogenetic molecules to just those cells and then to target the artificial stimulation appropriately. That is, if we knew the retinal code of "on" cells—the way they convert visual information into electrical pulses—as well as their molecular signature, these cells (or any other group) could be selectively targeted.

Here is how Nirenberg and Pandarinath accomplished this targeted approach in blind mice by making them carry a mutated version of a gene needed for photoreceptors whose ganglion cells also express ChR2. An encoder takes an image captured by a digital camera and converts it into a train of spikes appropriate to a particular group of ganglion neurons, for instance, "on" cells. It does this conversion from images into the retinal code by training and comparing its response with those actually recorded from "on" retinal ganglion cells. Thus, as a simple example, if a bright light had just moved into the field of view, the encoder should generate a burst of pulses. These signals are turned into pulses of blue light that drive the "on" retinal ganglion cells to fire a similar sequence of pulses. To the neurons in the brain proper that are the recipients of these "on" retinal ganglion cells, these pulses convey the datum that something luminous has just made its appearance [*see top illustration in box at left*]. Exploiting the same code as used by a healthy retina should help these blind mice see.

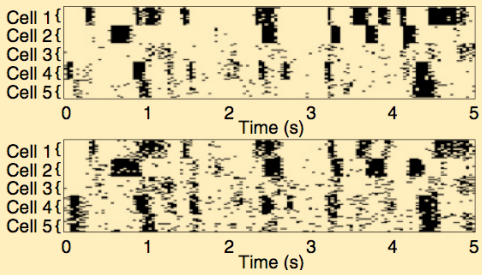
How well this device reconstructs pictures is shown in the images to the left. If the baby picture at the far left is sent through the device, the brain could, in principle, reconstruct the image at the near left. Far from perfect, but clearly the image of a toddler.

In a field test, actual mice outfitted with this retinal prosthetic could reliably detect motion to the left or to the right.

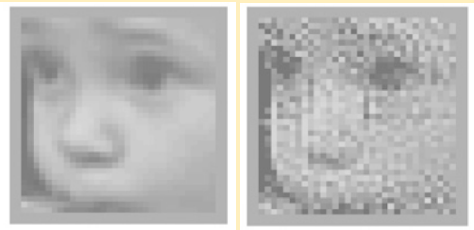
The true measure of performance, injecting a blind person's eye with viruses that express ChR2 in retinal ganglion cells and giving the patient a set of glasses that carries the encoder and light stimulator, is within reach. The fantastic marriage of molecular biology, optics and electronics that is optogenetics will soon bear fruit and help people regain their eyesight. Stay tuned. M

CHRISTOF KOCH is chief scientific officer at the Allen Institute for Brain Science in Seattle and Lois and Victor Troendle Professor of Cognitive and Behavioral Biology at the California Institute of Technology. He serves on *Scientific American Mind*'s board of advisers.

Vision Prosthetic



Signals from five ganglion cells (*top row*) are recorded from the retina of a normally sighted mouse looking at a movie of people walking, landscapes, and so on. The bottom row illustrates the response of five matched ganglion cells in a blind mouse fitted with an optoelectronic prosthetic device that stimulates the ganglion cells via light beams that excite the ganglion cells. The blind rodent's responses are similar to those of a normal mouse.



The image of a baby's face (*left*) is shown reconstructed from the spike trains, or signals, of a blind retina using a prosthetic (*right*). The reconstruction provides a measure of how well a blind mouse with its vision restored in this way would see the original 35- by 32-pixel photograph.

(Further Reading)

- **Interim Results from the International Trial of Second Sight's Visual Prosthesis.** Mark S. Humayun et al. in *Ophthalmology,* Vol. 119, No. 4, pages 779–788; April 2012.
- **Retinal Prosthetic Strategy with the Capacity to Restore Normal Vision.** Sheila Nirenberg and Chethan Pandarinath in *Proceedings of the National Academy of Sciences USA,* Vol. 109, No. 37, pages 15,012–15,017; September 11, 2012.

FROM "RETINAL PROSTHETIC STRATEGY WITH THE CAPACITY TO RESTORE NORMAL VISION," BY SHEILA NIRENBERG AND CHETHAN PANDARINATH, IN *PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES USA*, VOL. 109, NO. 37; SEPTEMBER 11, 2012