

Researchers Decipher the Retina's Neural Code to Create Novel Prosthetic Device

This strategy may have the capacity to restore normal or near-normal vision in patients with retinal degenerative diseases.

BY CALLAN NAVITSKY, ASSOCIATE EDITOR

More than 20 million people worldwide are blind or are facing blindness due to retinal degenerative diseases such as retinitis pigmentosa and age-related macular degeneration. These diseases result in a progressive loss of the retina's input cells, the photoreceptor cells, which leads to severe visual impairment. Despite this degeneration, the retina's output cells, the ganglion cells, remain mostly intact. Retinal prostheses make use of this by stimulating these surviving cells, driving them to send visual information to the brain. Current prosthetics, however, are somewhat limited in the vision they provide patients, as they generally produce only rough visual fields.

In a recent study published in *Proceedings of the National Academy of Sciences*,¹ Sheila Nirenberg, PhD, a professor in the Department of Physiology and Biophysics and at the Institute for Computational Biomedicine at Weill Cornell Medical College, and then-graduate student Chethan Pandarinath, PhD, hypothesized that the limitation of current retinal prosthetics may be the result of a coding problem. In response, the researchers worked to discover the code normally used by the retina to communicate with the brain and incorporated it into a high-resolution prosthetic device. In blind mice, the prosthetic enabled

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THE CODE

Prosthetic devices allow patients to see spots of light and high-contrast edges, which provide some ability for navigation and gross feature detection. However, these devices cannot yet provide patients with normal representations of faces, landscapes, and other detailed features. Recent attempts to improve retinal prosthetics have focused largely on increasing the resolution of the devices' stimulators.¹ Dr. Nirenberg maintains, however, that another critical factor is how to drive the stimula-

"The coded output combined with high-resolution stimulation makes natural vision restoration possible."

—Sheila Nirenberg, PhD

tors to produce normal retinal output.

"Briefly, when images enter the retina, they are transformed via retinal processing into patterns of action potentials," the researchers reported in the study.¹

"The patterns are in a code that the brain can read, a code the brain is expecting. Prosthetic devices have not yet incorporated this, raising the possibility that the reason they have not reached their goal is not just because of a resolution problem but also because of a coding problem."

The researchers reasoned that any pattern of light falling onto the retina had to be converted into a general code, a set of equations, that translates these light patterns into patterns of electric impulses. In addition, they knew it had to be generalizable, so that it could work for anything that a person sees, Dr. Nirenberg said.² While working on the code for another reason, the researchers realized it could be applied to a prosthetic device.

THE PROSTHETIC SYSTEM

The prosthetic system developed by Drs. Nirenberg and Pandarinath consists of 2 parts: an encoder and a transducer. The encoder, an input/output model of the retina, mimics the transformations performed by the retina: It converts visual input into the code used by the retinal ganglion cells. The transducer, the light-sensitive channelrhodopsin-2 (ChR2), then derives the ganglion cells to fire as the code specifies.

According to the study, the steps from the visual input to retinal output are as follows: (1) images enter a device that contains the encoder and a stimulator (a modified mini-digital light projector); (2) the encoder converts the images into streams of electrical pulses, analogous to the streams of action potentials that would be produced by a normal retina in response to the same images; and (3) the mini-digital light projector converts the electrical pulses into light pulses, thereby driving the ChR2, which has been put in the ganglion cells, to send the code up to the brain.

"This approach confers on blind retinas the ability to produce normal output, or patterns of action poten-

tials that closely match those produced by the normal retina," the researchers explained.¹

TESTING THE SYSTEM

To test the efficacy of the device, Drs. Nirenberg and Pandarinath presented movies of natural scenes to a normal mouse retina and recorded ganglion cell responses using a multielectrode array. They then recorded ganglion cell firing patterns from a blind retina when it was presented with the same movies, but this time, through the encoder-ChR2 prosthetic. Drs. Nirenberg and Pandarinath found that the spike patterns produced by the blind retinas closely matched those produced by the normal retinas.

"The reason this system works is twofold," Dr. Nirenberg said in a Weill Cornell Medical College news release.² "The encoder—the set of equations—is able to mimic retinal transformations for a broad range of stimuli, including natural scenes, and thus produce normal patterns of electrical pulses, and the stimulator (light-sensitive protein) is able to send those pulses on up to the brain."

The researchers also looked at ganglion cell responses from a blind retina viewing the movies through the standard optogenetic method, in which the visual input is presented without encoding. The movies were presented using the same stimulator so that the only difference between the approaches was the use of the encoder. They found that although the standard approach is effective in producing ganglion cell firing, the firing patterns are not the normal patterns.

"In sum, our results show that incorporating the code dramatically increases prosthetic capabilities," Dr. Nirenberg wrote.¹ "Although increasing resolution also improves performance, there is an inherent ceiling on the quality of image this can produce; adding the code breaks through this barrier. The coded output combined with high-resolution stimulation makes natural vision restoration possible."

FURTHER STUDY

Plans to test the device in humans in a clinical trial are currently in development, Dr. Nirenberg said in the news release.² Patients would receive an injection to implant the genes and would then wear eyeglasses outfitted with a camera and the mini-projector. A primary focus of upcoming studies will be evaluating the safety of the gene therapy component, which delivers the ChR2. ■

1. Nirenberg S, Pandarinath C. Retinal prosthetic strategy with the capacity to restore normal vision. *PNAS*. doi:10.1073/pnas.1207035109.

2. An artificial retina with the capacity to restore normal vision [news release]. New York, NY: Weill Cornell Medical College; August 13, 2012. http://weill.cornell.edu/news/releases/wcmc/wcmc_2012/08_13_12.shtml. Accessed October 1, 2012.