Scientists Look to Emerging Technology to Treat Chronic Neurological Disorders

Bridget M. Kuehn

SAN DIEGO—Scientists are finding potential therapies for chronic neurological disorders such as stroke and retinal degeneration by harnessing new technologies and a burgeoning understanding of human neurology.

Despite advances in neuroscience, cures for many chronic neurological conditions have proven elusive, leading scientists and clinicians to focus on potential rehabilitative therapies. To achieve this, many researchers are working to harness emerging electronic, computer, and molecular technologies to more specifically target the underlying genetic, molecular, and physiological deficits experienced by patients.

At the Neuroscience Meeting in San Diego in November, numerous scientists presented evidence that next-generation prosthetics and computer-assisted interactive therapies may improve function in persons with neurological conditions or in animal models of such disorders. Researchers showed, for example, that a noninvasive artificial retina could help restore near-normal vision in mice with damaged retinas.

In a healthy retina, the photoreceptors collect visual stimuli; the retinal circuitry translates these into neural signals that pass to the brain via the ganglion cells. But when disease damages the photoreceptors, there is no information for the still-healthy ganglia to transmit. Existing prosthetic retinas use electrodes surgically implanted into the ganglion cells to provide an artificial source of visual input to the brain. With such prosthetics, people can discern light and dark and distinguish edges, but they are unable to perceive images, explained Sheila Nirenberg, PhD, associate professor of physiology and biophysics at Weill Medical College of Cornell University in New York City, at the meeting.

Nirenberg and her colleagues hypothesized that the vision produced by prosthetics could be improved if the prosthetic could transform the visual image into the same neural code used by the ganglia. Over 10 years, the scientists learned the code by exposing photoreceptors to a wide array of visual stimuli and recording the responses of the ganglion cells. They then created a prosthetic device that uses the neural code and emits pulses of light. The team tested the system in retinas in vitro and in living mice with damaged retinas. In the mice, they used an optogenetic technique, a type of gene therapy that prompts the expression of light-sensitive proteins in the ganglion cells, so that the treated ganglion cells fire in response to the pulses.

BLIND MICE SEE

More than 25 million individuals around the world have impaired vision caused by degeneration of the retina.

Despite considerable effort, scientists have found it difficult to develop therapies that restore relatively normal vision to such persons. Now, with an artificial retina system that uses gene therapy and the language of the ganglia to communicate with the brain, researchers have produced near-normal vision in mice with damaged retinas.

Example of a fMRI of Brain Activation During Thought

Computers can be trained to recognize what a person is thinking about by comparing patterns of brain activation. For example, when a person thinks about hitting a tennis ball, the supplementary motor area and other regions are activated (blue), but when the same person thinks about moving from room to room, the parahippocampal place area and other regions are activated (red).
of light from the prosthetic. When the scientists tested the prosthetic device on these treated mice, they found that the ganglion firing patterns exhibited by these mice were nearly identical to the response of normal mice to the same image, while the firing patterns in the mice with the older prosthetic were very different.

If further testing in primates and humans is successful, the system might allow patients with retinal degeneration to see images as complex as faces, animals, or landscapes, said Nirenberg. She is collaborating on primate studies with William W. Hauswirth, PhD, professor of molecular genetics and microbiology at the University of Florida, who is developing optogenetic techniques for treating eye disease.

Another potential advantage of such a system for humans, Nirenberg said, is that the prosthetic does not require surgery. People using the system would have to undergo gene therapy, but the prosthetic itself could be worn like eyeglasses. The prosthetic could then be easily replaced with updated models as the technology improves. Nirenberg added that she and her colleagues are also working with companies that produce traditional retinal prosthetics to see if incorporating the neural code could benefit patients with existing implants.

VIRTUAL REALITY THERAPY

Using virtual reality–based video games and assistive machines, stroke patients who have lost hand function can improve their ability to use the hand and may increase the communication among regions of their brain, according to results presented at the Neuroscience Meeting.

Sergei V. Adamovich, PhD, associate professor of biomedical engineering at the New Jersey Institute of Technology in Newark, is working with physical therapists Alma Merians, PhD, PT, and Eugene Tunik, PhD, PT, both of the University of Medicine and Dentistry of New Jersey in Newark, to probe whether virtual reality video games and a robotic arm can improve hand function in stroke patients. The team recruited 24 patients who had a stroke at least 6 months before the start of the study. Patients underwent about 22 hours of practice using a virtual reality video game, in which they attempted such tasks as hammering a nail, picking up a cup, or playing a piano. When they reached the extent of their abilities, a robotic arm assisted them by providing some support against gravity, helping to stabilize their arm in the air, or pulling the arm forward to help the patient reach an object. Over the course of the training, the patients improved the speed of their hand movements, as measured by the Jepsen Test of Hand Function and the Wolf Motor Function Test.

The system offers advantages over traditional techniques. Merians explained that evidence suggests it takes many repetitions and intensive physical therapy to induce brain changes. In a traditional physical therapy program, a patient may do 85 repetitions of an exercise for about an hour per day, but with the assistance of the robotic arm, the patient may complete 2000 repetitions over 3 hours in a day.

“It allows more intensity and makes it more interesting for the subject to complete the training,” said Adamovich.

Analysis of brain activity in patients before and after the training suggest the program may indeed spur brain changes. A subset of 2 of the patients who completed the training while their brain activity was monitored using functional magnetic resonance imaging. The patients' brain activity after the practice was compared with 2 time points before the therapy. The researchers found increased connectivity among the bilateral sensorimotor and premotor regions of the patients' brains after training, suggesting that training increased communication among these regions.

The team is continuing the studies with larger groups of patients. In the meantime, patients who have completed the program have reported improvements in their ability to complete day-to-day tasks. Merians noted, for example, that one patient reported that without realizing it, she began cutting strawberries with both hands, something she had previously been unable to do.

TRAINING THE BRAIN

Another group presented evidence at the meeting demonstrating that a computer trained to recognize human thought patterns can enable individuals to manipulate a cursor with thoughts alone. The findings suggest such technology may one day be a useful tool for treating patients who have difficulty communicating, or may be able to help patients with addiction or other mental illnesses gain greater control over troublesome thoughts or urges.

Anna Rose Childress, PhD, director of the Brain-Behavioral Vulnerabilities Division at the University of Pennsylvania's Center for the Study of Addictions in Philadelphia, and colleagues enrolled 11 healthy volunteers and 3 patients under treatment for cocaine addiction who were abstinent in the study. Volunteers, while lying in a functional magnetic resonance imaging scanner, first completed a training exercise in which they alternated 30-second intervals thinking about hitting a tennis ball or moving from room to room in a familiar place. A computer programmed to use an algorithm to distinguish whole-brain activation patterns analyzed the individuals' brain activity, essentially learning to distinguish one thought state from another.

The training process took about 6 minutes. Then each participant again lay in the scanner and viewed a cursor on a computer screen. By thinking about tennis, the person could move the cursor up, and by thinking about moving from room to room, he or she could move it down. All of the participants were able to move the cursor.

Childress believes the technology may be useful for helping individuals with locked-in syndromes to communicate or for treating mental disorders such as anxiety or depression. But she is particularly interested in this kind of cognitive control, she explained, because patients with cocaine addiction have difficulty controlling crav-
Advances Reshaping Sickle Cell Therapy

M. J. Friedrich

IN 1910, JAMES HERRICK, MD, AN ATTENDING physician at Presbyterian Hospital and professor of medicine at Rush Medical College in Chicago, published the first case report of sickle cell disease (SCD), describing the “peculiar elongated and sickle-shaped” red blood cells from an anemic dental student from Grenada (Herrick J. Arch Intern Med. 1910;6:517-521).

Since that observation was made 100 years ago, the disorder named for these cells has become one of the best understood diseases at the cellular and genomic levels, leading the way for the scientific study of human genetics and molecular biology. And yet, as Susan Shurin, MD, acting director of the National Heart, Lung, and Blood Institute (NHLBI) in Bethesda, Md, pointed out, the most effective treatments for SCD—antibiotics, blood transfusion, hydroxyurea, and blood and marrow stem cell transplant—have been imported from the treatment of other conditions.

“While these therapies build on our understanding of the clinical manifestations of the disease, they really don’t exploit our molecular understanding of it,” said Shurin, who spoke at the James B. Herrick Symposium, “Sickle Cell Disease Care and Research: Past, Present, and Future,” held at the National Institutes of Health (NIH) in November.

But as many experts at the meeting noted, the field is entering an “exciting” phase that promises more targeted and tailored therapeutic solutions. Among the advances are new therapeutic targets to raise production of fetal hemoglobin, which eases the symptoms of the disease; new approaches to hematopoietic stem cell transplants that are rendering the molecular defect of SCD.

FIRST KNOWN MOLECULAR DISEASE

SCD was the first inherited disease found to be caused by a single amino acid substitution—at the sixth position of the β-globin chain of hemoglobin A. (The hemoglobin protein in the adult is a tetramer of 2 α-globin and 2 β-globin polypeptides.)

This simple substitution can wreak havoc in the body. Hemoglobin molecules with the defect have a propensity to link together and deform the red blood cells that harbor them. The resulting inflexible, sickle-shaped red blood cells can then clog small blood vessels and cause intermittent occlusion, giving rise to painful “sickle cell crises” characterized by pain, tissue damage, and anemia. Stroke, pulmonary infarction, and cardiovascular damage are some of the devastating clinical manifestations of the disease.

All individuals with SCD have the same mutation in the β-globin gene that gives rise to the amino acid substitution. Yet despite this genetic uniformity, the severity of the disease varies widely.

FETAL HEMOGLOBIN

One of the major contributors to this variation is fetal hemoglobin (HbF), the main form of hemoglobin in the body before birth. HbF is a tetramer similar to adult hemoglobin, with two γ-globin subunits in place of the two β-globin subunits. When the switch from

As a research tool, she noted, the technique may also provide valuable insights on what happens when individuals encounter powerful motivational stimuli. This might provide new targets for treating addiction or other disorders.

“We will be able to see in real time the brain’s struggle to stay in control when confronted with these powerful stimuli,” she said. □