Lighting up the brain

How optogenetics holds the potential to revolutionize the study of brain diseases such as epilepsy, addiction, and autism

Just a decade ago, some scientists were calling optogenetics a long shot, a crazy idea. Then it turned out to be not so crazy.

This relatively new technology allows neuroscientists to use light to probe the inner workings of the brain to study—and even control—pinpointed regions believed to be implicated in disorders like addiction, epilepsy, and autism.

The formula involves light-sensitive algae proteins, a detoxified virus (which acts as the rocketship that delivers the payload protein into the brain), and LED light (sometimes in multiple colors) administered via superfine fiber optic cables. (See sidebar on page 3: “How optogenetics works.”)

With support from MnDRIVE—an infusion of research dollars by the Minnesota Legislature into brain sciences, among other areas, at the University of Minnesota—and the federal BRAIN Initiative, a group of University neuroscientists is now all in on this groundbreaking work.

“One of the most exciting things about optogenetics,” says Patrick Rothwell, Ph.D., assistant professor in the
Targeting relapse

There’s a lot scientists still don’t know about the brain and its billions of neural connections. Over time, though, they have identified areas that seem to hold the key for disorders like addiction.

“If you think of the brain as a powerful computer, it has specific circuits dedicated to controlling particular functions,” explains Mark Thomas, Ph.D., associate professor in the Department of Neuroscience. “Studying morphine addiction in mice over time, we’ve identified brain circuits that are involved in a relapse-like phenomenon.”

Using optogenetics, Thomas has recently shown that he can retool those circuits, returning them to what he calls a “drug naïve state” – a discovery that could ultimately lead to treatments that would help people struggling with addiction avoid relapse.

“The challenge with addiction is to identify which circuits are really producing the addiction-like pattern of behavior so that, ultimately, we can target them with therapeutic intervention,” he says. “That’s what optogenetics, which is so exquisitely precise, allows us to do.”

Precise seizure control

Every day in the United States, doctors diagnose 500 people with epilepsy, a condition that causes recurrent seizures. Current treatments, says assistant professor of neuroscience Esther Krook-Magnuson, Ph.D., tend toward a “hammer” approach: drugs, surgical removal of brain tissue, and deep brain stimulation surgery, all of which can have unwelcome side effects because they can’t be focused intently on only the disordered circuits.

Using optogenetics, however, Krook-Magnuson can target the circuits with great specificity. In her lab, she monitors mice using brain electrodes and software that detects epileptic seizures. As soon as the seizure begins, the investigators shine LED light directly on to the targeted circuits, stopping the seizure.

“That specificity—seizure control without negative side effects—is what attracted me to optogenetics,” Krook-Magnuson says. “It’s like a classroom full of kids where only one is misbehaving. It doesn’t make sense to discipline the whole class.”

Zeroing in on autism

Rothwell, new to the U’s faculty this year, uses a different metaphor to describe his optogenetics work involving autism and addiction.

“Imagine the brain as an orchestra, with all of the cells working together. You might hear a problem...
How optogenetics works

The roots of optogenetics (optics + genetics) can be traced back to the 1970s, when scientists discovered that certain types of algae contained photosensitive proteins.

Jump forward several decades, when neuroscientists wondered whether, if they somehow put that algae protein into specific neurons in the brain, they could become light-sensitive. And could the scientists then control those neurons with light?

Vastly simplified, the answers were yes and yes.

To deliver the protein, scientists use a benign virus (one that won’t replicate or cause sickness), injecting it into the target cells of interest in the brain of a mouse. Those brain cells take up the virus—and thereby, the protein—while other neurons nearby remain unaffected.

Then, with a superfine fiber optic probe, the scientist shines LED light on to the target area and essentially turns on a particular set of neurons. Or they can use another protein that, once lit, inhibits the neurons from firing.

On a roll

The MnDRIVE and BRAIN Initiative funding were critical to producing this body of optogenetics knowledge, says Thomas, which is being shared with multiple labs across campus.

Now scientists are focused on the next steps: developing improved viruses to deliver the optogenetics proteins into the brain and using functional magnetic resonance imaging to actually watch what happens as the photosensitive neurons are activated.

“There’s so much promise here,” Thomas says. “Optogenetics has been a transformative tool, allowing us to work in the brain in a whole new way, to tackle the unknowns. And is it possible that it could be used as a therapeutic tool for humans? Yes, I think that’s on the horizon.”
With love from Rylee

A big sister sends a special ‘thank-you’ to her brother’s care team

For most kids, birthdays are a time for parties, cake, and presents. But when Rylee Routledge turned 7, she had a different kind of gift in mind.

Rylee’s little brother, Jake, had surgery in December 2014 for craniosynostosis—when the bones in a baby’s head fuse together too early, before the brain is fully formed. The surgery took place at University of Minnesota Masonic Children’s Hospital, under the care of neurosurgeon Daniel Guillaume, M.D., M.S., and plastic surgeon Martin Lacey, M.D.

“Jake’s surgery has made both of my daughters more compassionate and more aware,” says Shannon Routledge of Rylee and Raegen, who is 5. “They seem to be more empathetic in situations where someone may need more help or is not feeling well.”

Still, Shannon Routledge was amazed when Rylee, after seeing a TV ad for a national children’s hospital, announced that she wanted to send her birthday money to “Jake’s hospital” to help other kids. And Rylee didn’t balk when Shannon suggested that she ask friends coming to her birthday party to make a donation instead of bringing her a gift.

So after the party, Rylee sent $125 to U of M Masonic Children’s Hospital, along with a card and a sweet note: “I wanted to thank you for helping Jake and taking such good care of him.”

Proud parents Shannon and Darwin Routledge report that Raegen (and Jake, when he turns 2) are planning to follow in their big sister’s footsteps and donate their birthday gift money this summer as well.
For almost 2.5 million people living with multiple sclerosis (MS), simple exercise becomes a daunting challenge. The disease—which damages the central nervous system, including communication connections in the brain—brings disabling fatigue and, oftentimes, exquisitely sensitive body temperatures. Hop on a treadmill and work up a sweat? For those with MS, that can simply be an exercise in pain.

According to Adam Carpenter, M.D., however, there's increasing evidence that exercise actually induces changes in the brain, increasing the number of neurons and the size of blood vessels, and even improving brain function. Carpenter, a neurologist and assistant professor who splits his time between the Minneapolis VA Health Care System’s Brain Sciences Center and the University’s Department of Neurology, found himself wondering, could exercise help people who have MS?

"Most of the studies on exercise done to date tend to use very targeted strategies," says Carpenter, "but because people with MS are all over the map, from very active to very incapacitated, we decided to go a different route and ask, 'What happens if you just increase exercise?'"

Working with postdoctoral researcher Shikha Jain Goodwin, Ph.D., Carpenter designed a study, which has already enrolled eight veterans who have MS, that divides patients randomly into two groups: one that maintains their current level of activity and another that aims to increase their current level of activity by 100 percent. So if one person currently walks 3,000 steps a day, the study goal becomes 6,000 steps a day. There's no list of approved activities; rather, it's about maintaining or increasing whatever it is—walking, running, swimming, biking—that the participant already does.

As Goodwin explains, each participant starts with baseline magnetic resonance imaging and magnetoencephalography scans, which measure brain activity, as well as tests to evaluate cognition, fatigue, mood, neurologic disability, and overall well-being. Each participant is then given a wristband activity tracker; after four weeks, they return for reassessment and then continue at their assigned activity level for six more months. Carpenter and Goodwin decided to limit the study to six months because they don't want to discourage additional activity in the control group for longer than that.

"We're asking a lot of these participants either way," says Goodwin. "They have to be up for drastically increasing their activity level, or not changing it at all."

Because Carpenter and Goodwin are still seeking funding for a larger study, they'll keep this pilot program quite small. Ideally, though, they'd like to expand the work to give them a better survey of exactly what effects increased activity can have on people who have MS.

"Other studies have demonstrated that, yes, exercise can physically change brains in beneficial ways," says Carpenter, "but can it work in brains that have suffered damage from MS? That's what we hope to answer."

To learn more or find out how you can support this research, contact Eva Widder at 612-624-8650 or ewidder@umn.edu.
Once dragged down by the physical and emotional implications of Parkinson’s disease, man gets a new outlook on life after deep brain stimulation surgery

As his symptoms became more pronounced, the Tyks struggled with the disease’s implications. Patrick took so many medications to help control the symptoms that he says he felt “like a zombie” at times. Once, when he and Jo Ann were leaving a shopping mall, Patrick had to sit down on the curb because he just couldn’t make his body move across the parking lot.

It’s particularly painful for Patrick Tyk to recall the time he and his son, Carter, were getting ready to go to a hockey game, and Patrick had trouble buttoning his shirt. So Carter reached over and did it for him.

“I think about all of the times he did that for me as a child,” Carter Tyk says. “As the child, you don’t always take care of your parent in the same way, but it was something that I did, and it touched him deeply.”

Tyk’s neurologist in Brainerd, Minn., referred him to University of Minnesota Health to find out whether deep brain stimulation surgery, a procedure used to treat the symptoms of Parkinson’s when medications aren’t sufficient, could help him. After an extensive evaluation, the U team determined that Tyk would be a good candidate for the surgery.

Today, two years since his last surgery—he had two, one for each side of his brain—Tyk’s life has changed significantly.

“After the surgery, I felt strong enough that I actually went out and got a part-time job,” he says. “I do a lot of walking and physical exercise that I’m sure I never could have done without the surgery.”

Tyk still gets choked up talking about how much he appreciates the care he received at the U. “The DBS team was just fantastic. I can’t say enough about them,” he says.

Because of the surgery, Jo Ann Tyk says their outlook on life is a lot brighter. They spend less time worrying about nursing homes and more time fishing. “We look to the future,” she says. “Life is very good.”

Granddaughter Madisyn certainly has noticed the difference, too. “He’s smiling again. He’s happy,” she says. “He’s way more himself.”

Patrick Tyk—at far right, with (from left) wife Jo Ann, son Carter, and granddaughter Madisyn—is back to enjoying the simple pleasures of life.

Madisyn Tyk noticed that her grandpa wasn’t smiling as much as he once did. When she looked back at photos of them together, she thought Patrick Tyk always looked a little sad.

“I was really worried about him,” says Madisyn. “So I asked what was wrong—if he was OK and if he was happy. And they explained to me it was just the Parkinson’s mask.”

Patrick Tyk had been diagnosed with Parkinson’s disease in 2004 after his hands started trembling. In addition to the distinctive tremors and muscle stiffness the neurodegenerative condition typically causes, it can also immobilize the facial muscles, leaving the face constantly expressionless. That’s the Parkinson’s mask.

Patrick and Jo Ann Tyk had been planning to retire early, but they were overwhelmed with uncertainty after Patrick’s diagnosis. “It was almost like part of my life was over,” he says.
Refining research tools

U leads a multicenter project aiming to improve the technology needed to get better data on ataxia and Alzheimer’s disease

One thing that makes hereditary ataxias—devastating neurological disorders that cause progressive difficulty with walking, talking, swallowing, and eventually, surviving—hard to study is that they’re so uncommon.

And the fact that they’re tough to study makes them tougher to fight.

“There is a great need for reliable outcome measures with ataxias,” says Gülin Öz, Ph.D., associate professor at the University of Minnesota’s world-renowned Center for Magnetic Resonance Research. “Because they’re rare diseases, you don’t have the [large] patient populations that you can scan.”

But Öz and her team are hoping to overcome that hurdle with state-of-the-art magnetic resonance spectroscopy (MRS), a noninvasive technique that measures concentrations of different chemicals in the brain. Their project, which just won a five-year National Institutes of Health grant, aims to perfect software that could help in treatment trials of genetic ataxias—and ideally, other neurodegenerative diseases, too. Öz is leading the three-phase, multisite study.

Her team is refining commercially available MRS software so that it enables both researchers and clinicians to get higher-quality, more reliable results in people who have ataxia, for which early treatment can be critical.

“Once neurons in the brain die, you can’t bring them back,” Öz says. “But we’ve seen in animal studies that you can rescue those neurons if you intervene [soon enough].”

Potentially, their software could offer similar promise for treatment trials in Alzheimer’s disease and related disorders by detecting early chemical changes in the brain.

“When you’re testing a drug in a clinical trial, the drug may affect the symptoms but do nothing to slow down the progression of pathology in the brain,” Öz says. “So you need objective markers of the pathology in the brain, and the only way you can do that is with neuroimaging.”

In the study’s first phase, Öz and her team will work with colleagues at Johns Hopkins and Duke on automating and simplifying the MRS software.

Next, along with colleagues at Johns Hopkins, University of Florida, and Massachusetts General Hospital/Harvard, they’ll test the software’s efficacy in measuring brain chemistry in patients who have two kinds of hereditary ataxia, looking for consistent data quality at all four sites.

Finally, they’ll work with Mayo Clinic in Rochester, Minn., and the University of Michigan to see if the software can be generalized for use in treatment trials for Alzheimer’s, which affects different regions of the brain than hereditary ataxias.

When it comes to neurodegenerative diseases, especially ataxias, “there’s a big need here—a scientific need and a clinical need,” Öz says. “Moving our advanced MR technology closer to wider use is very exciting.”
The new, state-of-the-art University of Minnesota Health Clinics and Surgery Center opened its doors in February.

The 342,000-square-foot facility houses 37 medical specialties, as well as lab and imaging services, a retail pharmacy, a café, an outpatient surgery center, and other clinical services. Neurology, neurosurgery, and physical medicine and rehabilitation clinics are on the building’s third floor.

Housing so many specialties under a single roof promotes greater communication between the various medical specialists who may be part of each patient’s care team. In fact, the building incorporates several “collaboration spaces” for care providers to discuss patients’ care plans.

The Clinics and Surgery Center also makes prominent the latest research and medical innovations through its “Discovery Experience.” Visitors will find video monitors promoting clinical trials and other research opportunities in the center, as well as kiosks throughout the building that offer quick access to StudyFinder, a U of M website that highlights health research opportunities for both patients and healthy volunteers.

Other enhancements to the patient experience include an easier-to-access location (just off of I-94 on the eastern edge of the U’s East Bank campus), extended hours, convenient scheduling, and improved valet parking services.

Learn more at mhealth.org/clinics-and-surgery-center.