A MOVING STORY

SPINAL CORD STIMULATORS RESTORE HAND AND ARM FUNCTION AFTER PARALYSIS

BY MICHAEL AUBELE

ILLUSTRATIONS BY MICHAEL HIRSHON

No federally approved treatments are effective for treating paralysis in the so-called chronic stage of stroke, which begins approximately six months after a stroke incident. A team of scientists at the University of Pittsburgh and Carnegie Mellon University are working to change that. They've run successful tests on patients who had electric stimulators inserted along their spinal cord, resulting in significantly restored arm and hand function.

Heather Rendulic suffered five brain bleeds over 11 months as a college student and went from running 5K races and horseback riding to having to learn how to walk again. Half her body had become paralyzed from a cerebral cavernous malformation (CCM)—a group of tightly packed, abnormal small blood vessels in her brain that contained slow-moving blood that was clotted.

She was 22 years old and enjoying life at Indiana University of Pennsylvania when the series of strokes, which came without warning, upended everything for her. "I felt like my health was out of my control, and that I couldn't stop from bleeding again," she says. "I really struggled over that year. I was scared it could kill me, and the only way I handled it was taking things day by day and controlling what I could."

LEFT TO RIGHT: **Douglas Weber, Elvira Pirondini and Marco Capogrosso are leading the breakthrough study with stroke patients. Study results for the first set were published in Nature Medicine in February 2023.**

There are different types of CCMs, including those that form on their own and those that are hereditary. Rendulic had the first kind, which she describes as "just bad luck." Until those small strokes happened, she had no idea she had a CCM.

Doctors told her surgery would put her life at risk because the CCM was buried so deeply in her brain. But surgery "was the only known cure," she says, which meant that she would remain at risk for further bleeding and strokes.

The last stroke proved to be nearly fatal. "My entire left side was paralyzed after the fifth bleed, and it took me nearly two years to learn how to walk again," she says.

As catastrophic as it was, the stroke produced one positive result: It pushed the CCM to a portion of her brain where it could be removed more safely.

That was about 11 years ago, and between now and then, Rendulic has refused to let her condition get in her way. A woman of faith, she believes there has been a plan to all of this and that a "Why me?" attitude would be more damaging than any physical limitation. She finished college and began working full time. And she wrote the book "HeadStrong: Through Life, Love, and Brain Surgery." (Learn more about her perspective at heatherheadstrong.com.)

But Rendulic had no inkling during her recovery that living in the Pittsburgh region would position her to take part in a study that could eventually give hope to others who'd experienced paralysis from stroke: She agreed to undergo experimental surgery in 2021 to temporarily restore function to her left arm. It worked.

That pinnacle achievement in stroke paralysis therapy has its origins in a research lab in Switzerland.

Marco Capogrosso started working on his doctorate in biomedical engineering in 2009 at the Sant'Anna School of Advanced Studies in Pisa, Italy. He focused his research on mobility in patients paralyzed because of spinal cord injuries.

After earning his PhD, Capogrosso began postdoctoral research at the Swiss Federal Institute of Technology in Lausanne (EPFL), publishing the results of studies on restoring gait and balance after spinal cord injury. The therapy, which involved computer simulations and animal testing in rats, used electrical stimulation through spinal implants to restore movement. The studies moved from rats to primates to clinical trials with humans, with Capogrosso very much at the center of it all.

While he was at the EPFL, Elvira Pirondini showed up. She was investigating mechanisms of stroke recovery to understand why a stroke leads to hand paralysis and also exploring strategies to recover hand function. Pirondini's mentor in the lab was Silvestro Micera, who'd mentored Capogrosso at the Sant'Anna School of Advanced Studies. Micera had launched this second lab at the EPFL.

Pirondini says, "While Marco was working on computer modeling, I was working on robotics. I was watching his experiments, and he was watching mine."

"While talking at dinner," adds Capogrosso, "we realized that many of the mechanisms that were making stimulation effective for SCI [spinal cord injury] could actually work in stroke, and possibly even better than in SCI."

Their worlds collided in pursuit of restoring arm and hand function in stroke patients.

And something else happened. Capogrosso and Pirondini developed a romantic bond. They're now married with a child and on the faculty at Pitt; their personal and professional lives have intertwined. He is an assistant professor of neurological surgery. She's an assistant professor of physical medicine and rehabilitation and of neural engineering. When they walk from Oakland to their home in Point Breeze, they fre-

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TOP LEFT: Capogrosso (right) and neurosurgeon Peter Gerszten monitor the surgery on Heather Rendulic in May 2021. BOTTOM LEFT: A team led by Gerszten successfully implants two electrodes along Rendulic's spinal cord by threading them through openings between vertebrae. The electrodes (shown) are 5 centimeters long and, when activated, deliver electric charges to specific locations along the spinal cord. Those bursts of electricity allow patients to accomplish desired movements.

quently spend that time comparing notes.

It was Douglas Weber, a PhD and the Akhtar and Bhutta Professor in mechanical engineering and neuroscience at Carnegie Mellon University, who brought the couple to Pittsburgh.

Weber, who was on the faculty at Pitt before moving to CMU in 2020, had crossed paths with Capogrosso and Pirondini at various conferences and knew Micera well through professional connections. Sometime around 2017, he began to think that because Capogrosso and Pirondini were proving themselves to be rock stars in their field (with an excellent mentor in Micera), that he should recruit them to Pitt's Rehab Neural Engineering Labs. The process took a while, but the researchers arrived in Pittsburgh in 2020.

Soon after Capogrosso and Pirondini came to Pitt, a collaboration with Weber and a larger team of researchers took off, leading to the first clinical trial to use spinal implants to treat arm and hand paralysis in stroke patients. In 2021, with National Institutes of Health funding, they enrolled two patients, including Rendulic.

In May 2021, neurosurgeon Peter Gerszten threaded two small electrodes, thin and long like spaghetti strands, through a small incision in Rendulic's upper back and positioned them in the epidural space over the spinal cord in her neck to engage intact neural circuits.

"I wasn't nervous about the surgery from a safety perspective," says Rendulic. "I knew it was a safe procedure and involved very little risk. But even though my gut was telling me it would work, I was still a little nervous. I didn't want to let anybody down."

The result: For the first time in years, Rendulic was able to fully open and close her fists, lift her arms above her head and cut her own steak.

Prior to the implant, Rendulic had very little movement in her left arm. The stimulation gave her the ability to do everyday tasks she thought she would never do again.

Then in October 2021, Gerszten, an MD and Pitt's Peter E. Sheptak Professor in Neurological Surgery, did the same with the other trial participant.

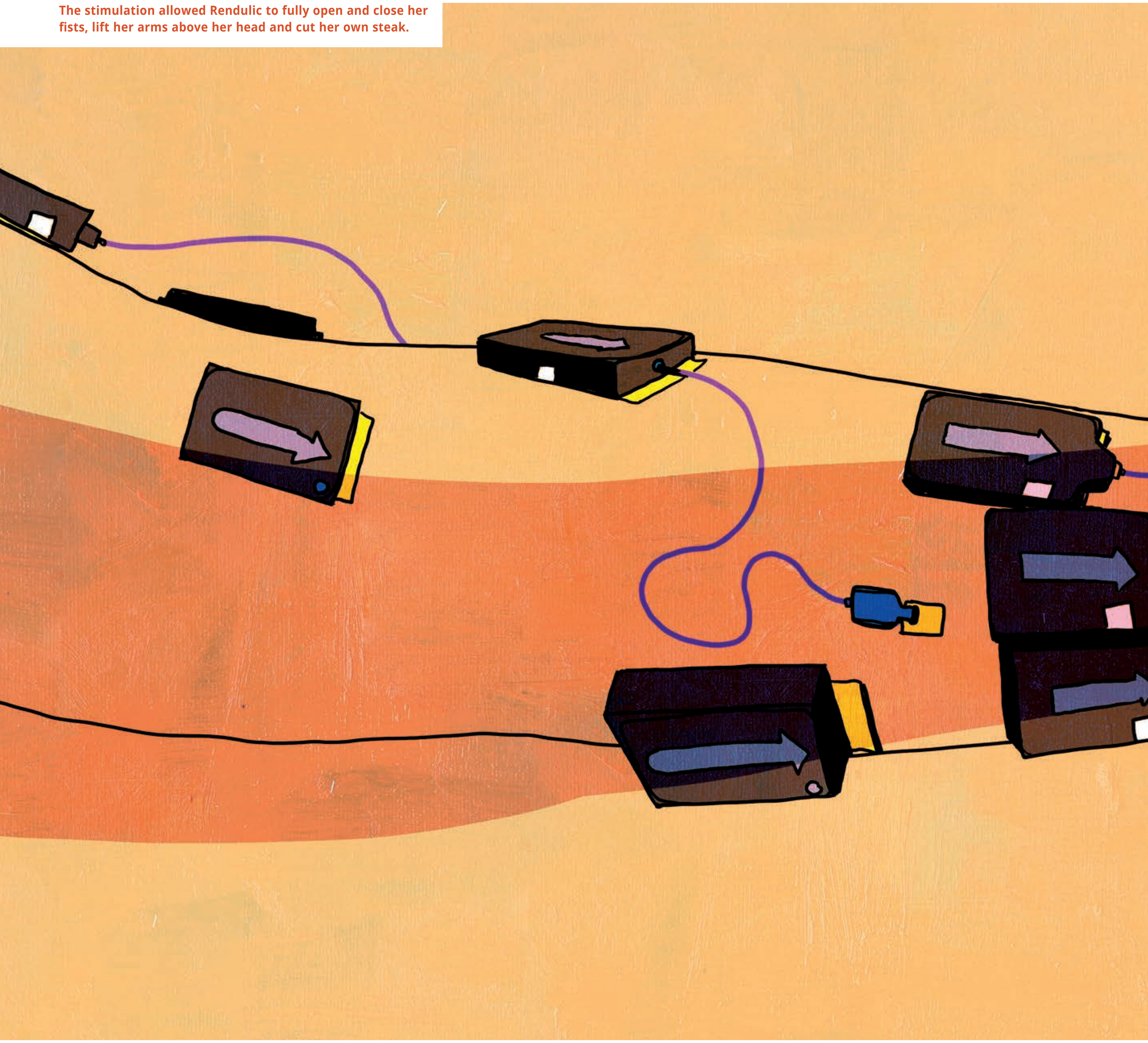
Like Rendulic, that woman experienced marked improvement in arm and hand function. She was able to extend her arm and remove a hollow cylinder from a wooden dowel and place it over another.

Because the woman's deficits were more severe than Rendulic's, her movement wasn't restored to the same extent.

The implant technology delivers pulses of electricity to activate nerve cells inside the spinal cord. Such stimulators have been on the market for years to treat other conditions like high-grade, persistent pain. Those electrodes, however, are placed lower on the spinal column. Additionally, the technology has been shown to restore movement to the legs after spinal cord injury; this is work Capogrosso pursued in Switzerland. Other labs have been working on this, too.

But the unique dexterity of the human hand, combined with the wide range of motion of the arm at the shoulder and the

The stimulation allowed Rendulic to fully open and close her fists, lift her arms above her head and cut her own steak.

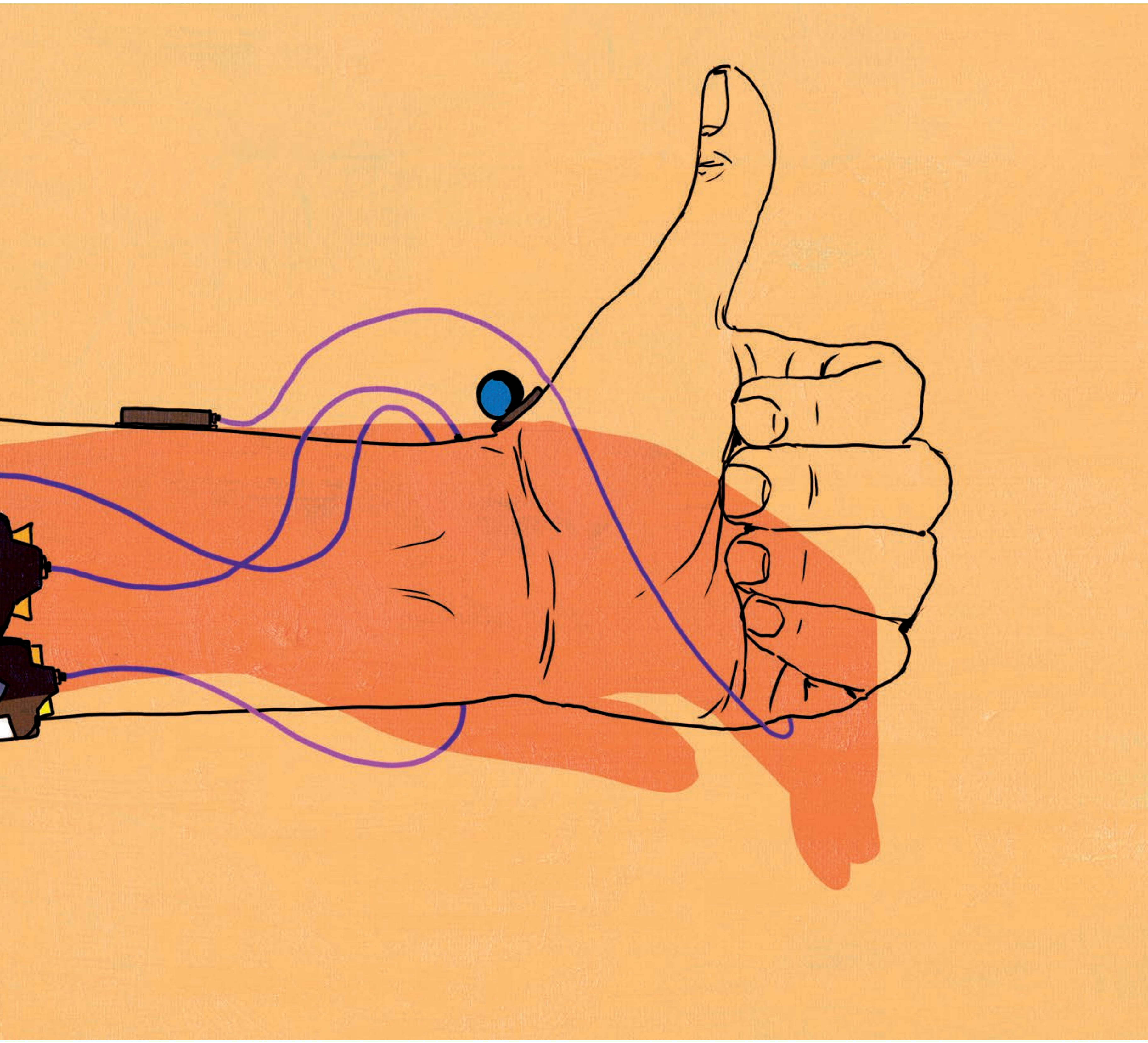


complexity of the neural signals controlling the arm and hand, add a significantly tougher set of challenges.

"The sensory nerves from the arm and hand send signals to motor neurons in the spinal cord that control the muscles of the limb," says Weber. "By stimulating these sensory nerves, we can amplify the activity of muscles that have been weakened by stroke. Importantly, the patient retains full control of their movements." The stimulation strengthens muscle activation only when patients are trying to move.

"The movement was so much easier," Rendulic says. "To feel like you have control is such a surreal experience, especially after going nearly a decade without moving your arm or your hand."

The researchers hope that the approach can do the same for other patients who've also had moderate to severe strokes. The team will be completing clinical tests on a total of eight patients using the NIH funding; they expect to conclude their studies in the fall 2024.



"We discovered that electrical stimulation of specific spinal cord regions enables patients to move their arm in ways that they are not able to do without the stimulation," says Capogrosso.

There was an unexpected benefit, as well: The team learned there could be lasting mobility improvements. "We found that after a few weeks of use, some of these improvements endure when the stimulation is switched off, indicating exciting avenues for the future of stroke therapies."

Capogrosso and team published the trial results for the first two patients in Nature Medicine in February 2023.

When it comes to strokes, cardiologists predict a grim future: Globally, one in every four adults over the age of 25 will suffer a stroke in their lifetime, and 75% of those people will have lasting deficits in motor control of their arm and hand, severely limiting their physical autonomy. Currently, no federally approved treatments are effective for treating paralysis in the so-called chronic stage of stroke, which begins approximately six months after a stroke incident.

"Creating effective neurorehabilitation solutions for people affected by movement impairment after stroke is becoming ever more urgent," says Pirondini. "With the increase of life expectancy [globally], it is estimated that these numbers will increase. And COVID-19, unfortunately, has contributed significantly to an increase in the number of people suffering a stroke.

"Even mild deficits resulting from a stroke can isolate people from social and professional lives and become very debilitating, with motor impairments in the arm and hand being especially taxing and impeding simple daily activities, such as writing, eating and getting dressed."

During this first phase, trial participants must be in the lab for their implants to be activated. Should all go according to plan with this first trial, the team will launch a second, longer-term trial to test the efficacy of an implant patients can use at home.

Based on the expectation that their trials will succeed, Weber, Capogrosso and Gerszten have launched a start-up called Reach Neuro to make the technology widely available for therapeutic use. Marc Powell, a PhD biomedical engineer who worked in Capogrosso's lab as a postdoc, serves as the company president.

"We started Reach Neuro because we realized there's a high likelihood the technology could be translated to the clinic," Capogrosso says. In the realm of biomedical breakthroughs, "your goal," adds Capogrosso, "essentially, is to build interest around your idea, and the only way to move forward is with a company that develops the technology with FDA approval"—in this case, for stroke therapy. Without that approval, doctors aren't able to offer the therapy to their patients.

"I live one-handed in a two-handed world, and it's frustrating because there are a lot of things you need two hands to do," says Rendulic.

It was two years ago, yet Rendulic vividly recalls the emotions she went through during her first day in the lab, as she began the trial spanning four weeks with the implant in.

"That very first day, none of us knew for sure if it was going to work, or how it would feel if it did," she says. "But that very first day in the lab, I opened and closed my hand for the first time in the nine years since my stroke. My husband and my mom were there, and when I opened that hand, there were just tears of joy.

"I probably cried every day in the lab for four weeks."

With the stimulation on, which she said felt like a tickle, Rendulic regained hand and arm function and could feel the sensation of making a fist and moving objects.

Rendulic's experience attracted a lot of attention. Local, regional and national media outlets, including The New York Times, USA Today and CNN, covered her story. People around the world have seen a video of her raising her arm over her head, rotating her wrist and picking up and moving a can of Campbell's soup.

The benefits of the stimulation remained somewhat after her temporary implants were removed. (She had a permanent implant in November 2021 for pain in her left arm.) She hopes that the FDA will ultimately approve the implants for stroke therapy, and that she can have a permanent device implanted for mobility.

"I wholeheartedly believe this technology can change millions of lives," Rendulic says. "So many people are affected by this.

"The future of this is so exciting. I know it will give me an added sense of independence."

Rendulic, thankfully, didn't experience any cognitive decline with her strokes. Her ability to return to school and graduate magna cum laude paid dividends. She's now a human resources executive.

"It actually has been a blessing," she says of her entire experience after her fifth stroke.

"It's more than 10 years out. I've written a book and have been able to do some motivational speaking. This really has opened doors for me to help people.

"My message has always been that we can't always control what happens to us, but we can control how we react to those situations." ■

—Anastasia Gorelova contributed to this report.

TOP: Researchers attach sensors that record the electrical activity of muscle tissue to Rendulic. **ABOVE:** Rendulic shows off her ability to pick up and move a can of soup, something she wasn't able to do with her left hand for nearly a decade after suffering a massive stroke.

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Capogrosso and Rendulic surrounded by the team that worked with her in the lab, including Pitt Med PhD students Erynn Sorensen (far left) and Erick Carranza (third from right).

BEHIND THE BREAKTHROUGH

Pitt Med students advance stroke recovery research

All Erick Carranza can figure is that his interest in disability research stems from a childhood experience.

It wasn't a traumatic one.

"No one in my family has a disability, but my whole interest in technology is helping people with disabilities," he says. "I remember seeing a cartoon when I was younger about a kid who had a prosthesis, and I was amazed by it. That was it, probably."

Growing up in Peru, Carranza said he was mesmerized by the science unfolding in developed countries, like the advancements in prostheses, which he used to consider the stuff of science fiction.

Coming to Pitt Med in 2019 with a background in robotic devices and automation, Carranza is now a PhD student working in the Rehab Neural Engineering Labs (RNEL), where he is advised by Elvira Pirondini, a PhD assistant professor of physical medicine and rehabilitation and of bioengineering. He's played an integral role in a stroke paralysis research study run by a team of Pitt and Carnegie Mellon University scientists that restored significant arm function to patients through spinal implants. (See "A moving story," page 24.)

"It's the person doing what they want to do as they want to do it, as opposed to something external doing it for them," says Erynn Sorensen, about her inspiration to be on the team. Sorensen is also a PhD student in the lab where she is advised by Marco Capogrosso, a PhD assistant professor of neurological surgery. She is a co-lead author on a paper published with Carranza and the Pitt/CMU team in Nature Medicine about the study.

No approved treatment exists for regaining hand movement in the chronic stage of stroke. The Pitt/CMU team's approach was to thread electrodes through the vertebrae of study participants, delivering electric charges to specific locations along the spinal cord and allowing the patients to make desired movements.

Sorensen joined the lab to merge her neuroscience background with a more clinical approach, and she and Carranza are among several graduate students and trainees who've taken leading roles on the ongoing study—including Souvik Roy (MD '23), who was completing a research fellowship, as well as students from the Swanson School of Engineering and CMU. Along with evaluating whether the device helps patients with their movements, Sorensen helps to run experiments and coordinate them. Carranza's main role has been developing and assessing tasks during which patients use a Kinarm, an exoskeleton that supports the patient's arm and measures movement (while the nerves are stimulated through the implanted electrodes).

Each patient's disability is distinct, so developing appropriate tasks for them to attempt can take days of fine-tuning. "We customize the task to each patient's limitations and try to challenge the patient to do things they can't normally do," Carranza says.

The project has reinforced his desire to work at a company that uses technology to help patients affected by stroke or other neurological diseases. "I have never seen a technology before that makes such a big difference in such a short period of time," he says. "If I can do this for the rest of my life, that would be so cool."

—Michael Aubele

—Patrick Monahan contributed to this report.