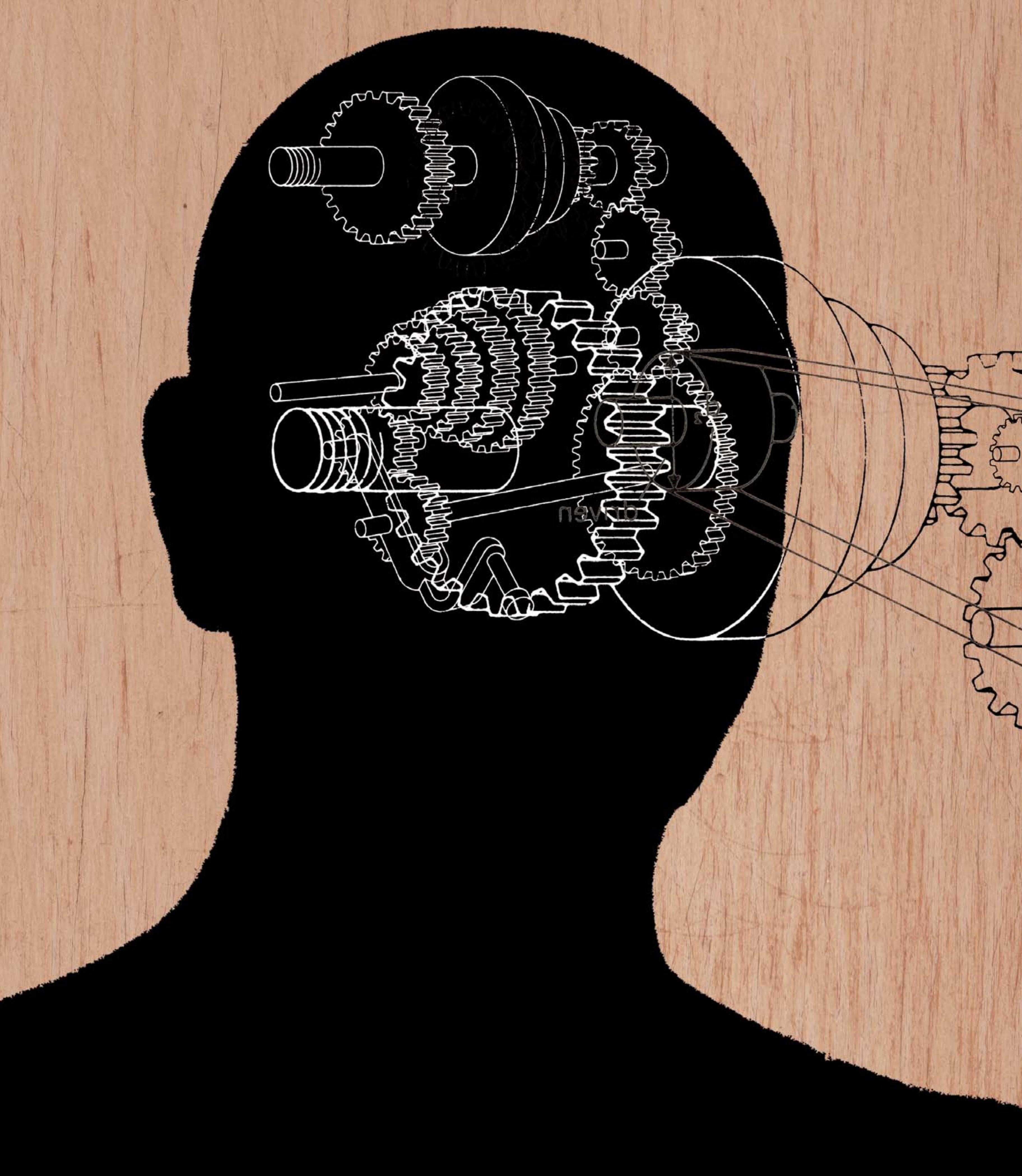
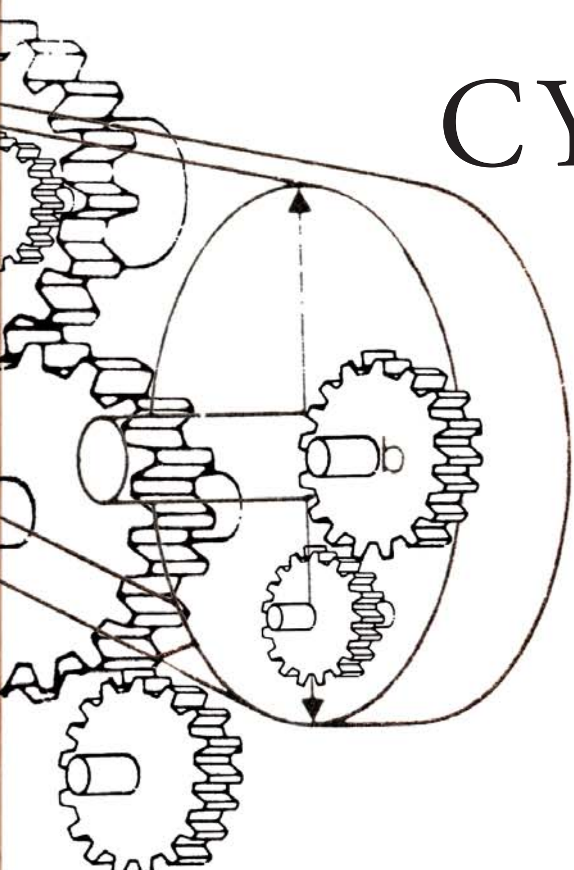


COMPUTER-BRAIN INTERFACES AND OTHER PRAGMATIC VISIONS

BY ERICA LLOYD



CYBORG MEDICINE

"That's good. What's that? Is that internal rotation?" asks Andrew Schwartz, who's standing next to a workstation outfitted with Yamaha speakers, a recording system, and a lode of computer and video screens.

A crackling electronic noise is his object of intense interest. With each crackle, a wave trips on a screen, like a seismograph detecting a tremor of the earth. Each crackle is a clue to what's happening in the brain of a monkey sitting in a room next door.

"Right there!" says Schwartz, as white-coated technician Ingrid Albrecht records each hit.

More crackling.

"There."

Crackle!

"There," he says.

Crackle.

ILLUSTRATIONS | DAVID POHL

"Okay, that's good. All right. What's that now?"

"Abduction," says Albrecht after getting up from her chair at the workstation to peer through a cracked open door. She is relaying the answer to Schwartz's question from Edgar Ycu, another technician here at the University of Pittsburgh McGowan Institute for Regenerative Medicine. Ycu is just out of earshot, in the neighboring room, moving a monkey's arm in different ways. The crackling is the result of neuronal firings, what are called spikes, from the monkey. The spikes are made audible to Schwartz and the others by eight microelectrodes that Schwartz has surgically implanted in the monkey's brain through a quarter-size incision in its skull.

"AB or AD?" Schwartz asks Albrecht. He wants to clarify whether the movement is abduction or adduction, that is, whether Ycu is guiding the monkey's arm away or toward its body.

"AD?" Albrecht asks Ycu. Nope.

"AB. Abduction," Albrecht reports back.

"Okay, that's about it. That's good, Edgar. We're going to let him rest for a while. Can we give him some food? Give him monkey chow."

This is their second day exploring the topography of the monkey's primary motor cortex (so called since scientists in the 1800s discovered that electrical stimulation to that area of the brain produced movement). So far, the crackles have told the researchers that the electrodes are in the region that controls the shoulders and elbows, which is where they want to be. This process allows them to find the hot spots of interest in the brain, before Schwartz—a neuroengineer, Pitt professor of neurobiology, and faculty member in Pitt and Carnegie Mellon University's Center for the Neural Basis of Cognition—implants an array of permanent recording microelectrodes.

Around the corner, at another workstation, a technician monitors the ability of a monkey in a neighboring room to control a cartoon cursor ball in a virtual reality 3D environment. Monkeys are pretty clever; it's not so strange that you can teach one to play such a game. But this monkey is not using its hands. This monkey is sitting in a chair and moving the cursor ball just by thinking about it.

The monkey seems to be doing pretty well. Its cursor ball starts in the middle of a cube and then "reaches" to the corners. When it hits a target, the monkey is rewarded with a drink of water.

Monkeys that play this game in Schwartz's lab usually have graduated from using their actual arms in the 3D environment. (In this version of the game, the cursor is tied to the back of the monkey's hand.) They play the game this way for about four weeks. Eventually, Schwartz's techs restrain the monkey's arms and, with microelectrodes in place, see what happens. The monkey always learns to manipulate the cursor with no hands. And, as it turns out, even when the monkeys don't start playing the game by using their hands to move the cursor ball, they figure out how to move the cursor with mere thoughts.

As a monkey plays these 3D games, Schwartz's team records the firings emitted by neurons that are in contact with the microelectrodes.

While he gives a tour of his lab, Schwartz notes that he started these studies with one electrode; now he can use as many as 16. As he reports this, he walks with more spring in his step. The combination of Schwartz's runner's build, high forehead, and small wire glasses conveys energy most of the time. And the possibility such microtechnology holds gets the 48-year-old more charged. "It took a long time to get to this point," he says. His lab has been working on this for more than 10 years. (The first time neuroscientists implanted an electrode to monitor the activity of a brain cell in an active monkey was in the '60s.) By using an array of microelectrodes, Schwartz's lab is monitoring the activity of several groups of neurons at once.

Miniaturized technology used by his and a few other labs has allowed scientists to see more than one part of the brain at a time, leading to new insights on fundamental issues like causality. Scientists hadn't the tools before to determine, for instance, what influence one neuron might have on all the other parts of the brain. "We're within the range of being able to answer these questions," Schwartz says.

Neuroscientists carry some baggage regarding the motor cortex, though. For some time, it was thought a given neuron moved a given muscle. This is not the case. Many neurons are involved in moving any one muscle. And a given neuron is likely to be involved in moving lots of muscles. "It's not a push-button switchboard hypothesis, where you turn on one cell and you get a muscle twitch," says Schwartz.

But some would still rather study one cell at a time instead of populations, says Apostolos Georgopoulos, who has at least six prestigious titles at the University of Minnesota, including the McKnight Presidential Chair in Cognitive Neuroscience. Georgopoulos was Schwartz's postdoctoral fellowship adviser in the '80s at Johns Hopkins University, where the senior investigator first got neuroscientists talking about neuronal activity in terms of cell populations. He would liken investigators who disregard the population approach to those who were duped by one of the most notorious pranks in collegiate history.

On January 2, 1961, a capacity crowd in Pasadena, Calif., filled the Rose Bowl Stadium. They were there to watch the University of Minnesota Golden Gophers take on the University of Washington Huskies. At the signal of the Washington cheerleaders, the Husky fans had been instructed to lift colored cards. The plan: They would spell WASHINGTON in letters a few stories high across the stands, making their school pride evident to the opposing team as well as millions of NBC television viewers. In the first half, the Huskies charged ahead, gaining 17 points while Minnesota failed to score. The ebullient Huskies in the stands rejoiced during halftime and, at the cheerleaders' signal, raised their cards to spell, unwittingly, the name of the nearby engineering college that had never been invited to the Rose Bowl, CALTECH. In an elaborate hoax, a gang of Caltech students had studied and infiltrated the card cheer plans. But the Washington fans were too busy holding their individual cards as directed to realize what had happened. They kept smiling while the Washington cheerleaders, who could, of course, see all the cards

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from the field, stood in shock.

To understand how any part of the brain works, you need to pay attention to a lot more than one card at a time—and you need to keep watching.

"You want to know what combines with what and how things interact," says Georgopoulos. "The biochemistry changes. Behavior, emotion, these are time-varying conditions. That's the essence of the brain."

Figuring out the roles of neurons involved in motor control gets even more complicated if you think about the intricacies of how we move in space. Consider the small spatial acrobatics an arm performs when doing something as simple as reaching for a glass of water (or raising a card in a Pasadena stadium). Consider how the shoulder reaches, the arm extends, the wrist twists. Schwartz's kingdom is the nuance of such everyday feats.

Yet Schwartz says that scientists can't tell you much of anything with precision about how the brain makes such actions happen.

"There really isn't anything we can point to and say, 'We understand how the brain does this.'" Even in the heavily studied visual cortex, he insists, "you cannot point to a single thing in the brain and say, 'Oh, we understand how the brain creates an image or how you see something.' We don't." After 20-plus years of study, Schwartz doesn't pretend to understand how the motor cortex functions, either. (And these operations must be small potatoes compared to how "higher-level" operations like thinking happen, he points out. As he sees it, anyone who tells you neuroengineers are on the brink of enhancing memory or math skills or other cognitive functions is serving up pure bunk.)

But how could he understand the motor cortex's precise role in 3D movement when no one knows all the muscles engaged during a seemingly simple movement like a bicep curl, he asks, demonstrating a curl himself with his arm extended. "It may be 90 percent bicep, but what else?

"Now let's say you're doing *this,* okay?" he says, making a similar movement with his arm next to his body. "Where you're flexing your shoulder and your elbow at the same time—it could be a completely different set of muscles."

He intends, however, to find out which muscles are involved in certain activities. His lab is refining a study in which the arm movements of human subjects in a virtual reality 3D setting will be tracked with highly sensitive sensors.

"If we want to do this for a paralyzed person, to activate their arms," he says, "we should understand what the natural way is of doing it so we can replicate that."

Schwartz spurs his lab on to accomplish a whirlwind of nonpedestrian feats. Need a virtual 3D environment? Build one. Need to understand the muscles in the arm like no one has before? Figure out how.

"He delivers," says Georgopoulos, who believes Schwartz is "just ramping up."

Last year, he delivered, in the form of a paper in *Science,* his finding that the illusion of movement and actual movement are governed by different parts of the brain. (See "It's an Illusion," on p. 27.)

Computer-brain interfaces may one day help people with disabilities; that work has already begun in experimental stages. Such technology will also tell us a great deal about the human brain.

His studies have also shown that what happens in the motor cortex when a primate performs a task (like the virtual reality game) using thought control is not necessarily the same as what happens in the motor cortex when the primate uses its own limbs. The same neurons may be employed, but to a greater or lesser extent.

In the '80s, when Schwartz was graduating with his PhD in physiology from the University of Minnesota, he appealed to Georgopoulos, who was then at Hopkins, to let him train in his lab. Georgopoulos asked the would-be postdoc to describe himself.

The answer: "I'm just an honest guy from Minnesota." Georgopoulos laughs about that today. Schwartz has great integrity, he confirms; in fact, he says, his "star fellow" is so honest, he can get himself in trouble. Schwartz, who considers himself an experimentalist, has been known to tell a dinner table full of theorists, "It must be nice not to be bogged down by data." Then he'll chuckle, and others will join in. Besides being an honest Minnesotan, he's also a pragmatist. Yet he's a pragmatist with real vision. Georgopoulos credits him with bringing their field into the 3D realm, seeing the potential for how this science might one day help people with paralysis, and taking the steps—in particular, applying microelectronics—to begin to make that happen.

Schwartz may be a pragmatist, but his is a world without the boundaries you and I are used to.

Using thoughts to control objects, that's old hat around his lab. The dialogue here sounds almost spooky: "I want to implant electrodes in people's brains to help them," says one of Schwartz's graduate students, Marshall "Chance" Spalding. He may be able to realize that dream one day, but on this September day, he's working with postdoc Meel Velliste to refurbish a robotic arm that a monkey will use to feed itself just by thinking about it. Schwartz has already succeeded in getting two monkeys to manipulate a robotic arm in this way.

Watching a video of a monkey feeding itself with the robotic arm, it's striking how natural the movements appear. There's little jerkiness that you might expect from watching robots featured in popular media. The robot arm doesn't make choppy movements like the arms of one of George Lucas' battle droids. Instead, its extensions and contractions are fluid, reminiscent of how a monkey might actually grab a piece of orange and place it in its mouth. By capturing the spikes created by populations of cells at regular millisecond intervals and interpreting them, Schwartz's team has translated the monkey's brain firings into fluid prosthetic movement.

In fact, the robotic arm seems to adhere to what are known as the invariant rules of movement. Invariant rules explain why we tend to, for example, slow down when we come to a sharp curve as we draw an oval. They explain why my arm movement is slow as I begin to reach out for a glass, then reaches maximum velocity halfway to the glass, then slows down on my approach a couple of inches from the glass.

All animals follow these invariant rules, Schwartz points out, even octopi—who get around using propulsion, rather than manuvering joints.

The monkeys successfully fed themselves with the robotic arm, yet they can do better, Schwartz believes, with a better robotic arm. The arm, handmade in China, had a lot of play around the joints and some questionable wiring. It didn't respond with precision. After refurbishing, the arm will have better cables, new sensors, and other updates. Although there may be a few kinks to work out, it is shaping up nicely, says Schwartz, as he proudly displays the newly installed cables and moves the elbow joint.

In the past, the monkey managed half the job of feeding itself. A human placed the orange in its robotic gripper. (The prosthesis has three simple nonbending digits for gripping rather than a full set of fingers.) With a more precise robot arm, the hope is the monkey will be able to grab the orange itself. And getting the human out of the room will be less distracting. Monkeys are fascinated by human facial expressions and like to interact with us.

There's some healthy anxiousness about having the robot arm ready in a month or so for a conference in San Diego, where Spalding and Velliste are expected to make a poster presentation and star in a press conference.

"Will it be ready?" they're asked.

The answer might not satisfy their boss, yet it is in line with his pragmatism.

"There's working, and there's working better, and then there's working well, and then there's working real well," says Velliste.

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Johnny Ray, of Carrollton, Ga., played the guitar and made a living installing drywall before he suffered a devastating stroke at the age of 52. Though his intellect was intact, the stroke left him unable to move or communicate with the world. He became locked in his own body.

One thing Ray had in his favor was living not far from Philip Kennedy, a Dublin native, MD/PhD, and CEO of Neural Signals in Atlanta, who believed he could help Ray. He'd developed a miniature electrode, encased in glass, which had won FDA approval for implantation in human brains. (His microelectrode was the first, and now is one of perhaps three, to be so approved.) Kennedy hoped that by implanting electrodes in Ray's brain, the man would be able to communicate through a tailor-made computer interface.

For the first three months after implantation, fibrils from Ray's nervous system grew into the electrode. (Kennedy's electrodes are designed to become one with the brain in this way.) Then Ray spent about a month of daily 20-minute training sessions learning to control the cursor. One day, Kennedy asked him to spell his own name. By moving a cursor across a screen of letters, Ray managed to spell JOHN twice in just four tries.

He took a break and tried again.

JOHLQQQ.
GYUVWABDN.
HIJJROHNLN. JOIH.N.

When he began moving the cursor over to the P, Kennedy thought he'd let him rest.

But then, Ray spelled PHIL, Kennedy's first name.

"It was very exciting," says Kennedy.

Ray has been called one of the first cyborgs. His architect, Kennedy, is visibly humbled by accolades sent his way for his achievements, like *Discover* magazine's award for assistive technology. Kennedy had hopes that, through the computer, Ray might be able to create music again, perhaps even run an Internet business. Ray's activities didn't progress beyond spelling and clicking icons (designed with locked-in patients in mind, so that a patient could control the heat in his room or convey other complex ideas quickly), yet the electrodes continued to serve Ray for more than four years, until he died of a brain aneurysm in 2002. (The basilar artery at the base of his brain was weak from his stroke, causing a blockage of fluid and fatal swelling.)

Since Ray was implanted, four other Kennedy patients have been as well. (One other patient used the brain-computer interface before Ray.)

As this story was finalized, Schwartz and Kennedy were about to embark on a collaboration that would combine their technologies. They plan to use Kennedy's FDA-approved microelectrodes in a locked-in patient who will experiment with Schwartz's virtual reality 3D environment. After that, they'll consider giving such a patient access to a robotic arm.

Schwartz divulges news of the collaboration without grandeur, as though this were simply the logical outgrowth of his efforts. He's clearly pleased, but expects more from himself and the field. If such prostheses are to be used widely by quadriplegics, they'll need to offer finger dexterity, he believes. "And why not work toward using a patient's own limbs?" he asks.

The field of neural engineering is fraught with dashed hopes. So Schwartz proceeds with discretion. It's easy to see how such projects can capture our imagination. This is the stuff of made-for-TV movies, literally. In the '80s, CBS ran a docudrama about an Ohio undergraduate who was paralyzed from the rib cage down. Working with Jerrold Petrofsky, a physical therapy researcher then at the same university, she learned to use a computer-driven interface that sent a pattern of electrical pulses to her legs. With Petrofsky and another professor at each side, she eventually "marched" a few tentative steps in her commencement ceremonies using the technology.

The docudrama and other media reports of the woman's march brought the National Institutes of Health a flood of letters from paralyzed people and their families wanting to know how they could benefit from this technology. The woman marched before an audience again, down the aisle at her wedding, years later, yet these and similar feats by other patients have still not translated to anyone tossing aside her wheelchair for good. (Though some patients were eventually able to walk miles with another evolution of the technology.) Petrofsky, the inventor who is now at Loma Linda University in California, says that it would have cost millions to get FDA approval for his walking system, so he decided not to pursue it. The application of this technology he's most proud of developing—has FDA approval—helps people with disabilities lift weights and ride exercise bikes. (These systems build endurance, strength, and cardiovascular health and combat atrophy.)

The flurry of press around that undergraduate's commencement march resulted in a group of neuroscientists issuing a joint statement cautioning the public on the experimental nature of such technology.

The Schwartz/Kennedy collaboration will be experimental as well, and Schwartz prefers to focus on the implications for fundamental discovery that we can expect in the long term from such research in humans:

"I think the really powerful part about what we are doing is we're coming up with new technology to record neural activity.

"I don't believe you can study cognition in any other animal besides humans. People have all of these theories about cognition and how it takes place, so now we're going to have all these opportunities to [actually test them]. I think we'll be able to do, in conjunction with this prosthetics work, some really interesting basic science experimentation that we've never been able to do before.

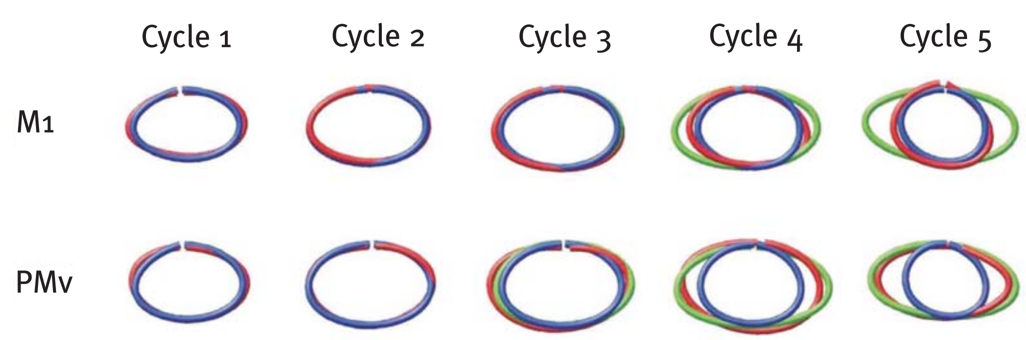
"I think the benefit to society from those scientific observations will far outweigh anything we do in prosthetics."

That said, it's hard not to be captivated by what his and Kennedy's efforts could do for people like the late Johnny Ray, for whom such technology means finally being able to communicate with the world again, or for others with less severe disabilities.

One possible candidate for the study is a man in his 20s whose movement, since a brain-stem stroke six years ago, has been limited to directing his eyes upward.

Both researchers are eager to push ahead. When Kennedy is asked in an e-mail if he has a timeline for when a patient will be confirmed for the collaboration, his one-sentence reply imparts a sense of urgency:

"I am working hard to implant as soon as possible." ■



IT'S AN ILLUSION

Andrew Schwartz can get you to move in a way that's different from how you think you're moving. This illusionist is a neural engineer at Pitt. In virtual reality experiments, Schwartz had people draw ovals and circles. When he presented volunteers with an image of the path of an ellipse, but subtly required their hands to move in a circular path, they still reported that they were drawing an ellipse. Time after time, people reported that they drew what they saw, rather than what they were actually drawing.

Schwartz did similar studies with monkeys whose neurons he monitored. You can't ask a monkey to report what it's doing, but data collected from brain firings show that the monkeys perceived they were drawing what they appeared to be drawing as well, even when they were drawing something else. The above figure demonstrates Schwartz's results. Blue represents the actual path of a monkey's hand. After the first two cycles, Schwartz makes slight changes in the gain of the cursor (shown in green), so the monkey must make more circular (and less elliptical) movements to keep the cursor on track. Yet throughout the experiment, the path the monkey is supposed to follow appears the same on the computer screen. By the final round, the monkey appears still to be drawing an ellipse—from what it sees on the screen—yet it has made the movement of drawing something much closer to a circle.

What do the brain firings tell us? Action and perception of action seem to be represented by different parts of the brain. The monkey's motor cortex (see M1) captures the impression of drawing a circle when the monkey actually draws a circle. (The neural trajectory is shown in red.) The monkey's ventral premotor cortex (PMv, its trajectory is also in red) stubbornly senses that an ellipse is being drawn. So it seems that vision is dominant compared with proprioception. And, it seems, you can't believe everything you see. —*EL*