PLUGGING BACK IN

Can brain-machine interfaces empower paralyzed patients?

by Janelle Weaver

"May the force be with you," says Lavi Secundo, a UC Berkeley graduate student, to a patient as she attempts to control a computer cursor using her thoughts alone. Surgically implanted with electrodes that record electrical activity from her brain, the patient simply has to think about moving her hand in a certain direction, like she's Luke Skywalker in *Star Wars*, to get the cursor to go the right way. Scientists at UC Berkeley hope that moving cursors is just a precursor to more meaningful independence for paralyzed patients: controlling a wheelchair, feeding themselves, and checking email may one day be within their grasp.

Nearly six million paralyzed Americans stand to benefit from such technology. Despite enhanced national awareness of the plight of paralyzed people and decades of research across multiple fronts, there is still no "cure." Once cells in the brain or spinal cord die, they generally do not recover. "Perhaps one day stem cell research may move us closer to a cure, but in the short term, the best we can do is improve patients' quality of life with brain-machine interfaces," says Secundo.

What is a BMI?

Brain-machine interfaces (BMIs) are devices that bypass damaged neurons, allowing intact cells to control computers and robots. They come in a variety of flavors, from invasive surgical methods to non-invasive electrode skull caps. Although non-invasive approaches can be used to control computer cursors and spell words (albeit slowly), invasive methods may be more powerful, since proximity to neurons yields a stronger signal. Some scientists believe that invasive approaches are necessary to achieve complex, natural movements with minimal training.

Currently, invasive BMIs are carefully restricted in human clinical research trials. Despite the scarcity of opportunities to employ invasive approaches in humans, there are already promising signs of their effectiveness. In a landmark 2006 study, John Donoghue and colleagues at Brown University demonstrated for the first time that a quadriplegic patient could check email, draw a circle, operate a television, play computer games ("Neural Pong"), and control a prosthetic hand and robot arm using an electrode array implanted into his primary motor cortex, a part of the brain that controls movement.

Scientists at UC Berkeley are also experimenting with invasive BMIs, but their approach is slightly different. Rather than working with paralyzed patients, who must agree to have electrodes implanted into their brains for research purposes, Secundo performs tests on epilepsy patients who already have electrodes on the surface of the brain.

Access to brain signals

Severe cases of epilepsy can require the removal of the brain's seizure "epicenter." In order to precisely localize the area to be lesioned, neurosurgeons first implant an electrode array to continuously monitor brain activity—a procedure known as electrocorticography (ECoG). Surgeons typically wait seven to ten days for a seizure to occur. This window provides the unique opportunity for researchers to record high-quality brain signals from humans as they perform cognitive tasks involving language, memory, attention and motor control.

Despite the challenges they face, patients are generally excited to contribute to the research effort. "We sometimes give them very boring tasks—they have to press buttons when they hear 'beeps' and 'boops'," says Secundo. "But the patients and families are very motivated and engaged, and we do try to make it fun for them, like a computer game," he adds.

Robert Knight is a professor of psychology, the Evan Rauch Professor of Neuroscience and director of the Helen Wills Neuroscience Institute. "BMI is a new area for my lab," he says. "We started three years ago, and now we have an active ECoG program."

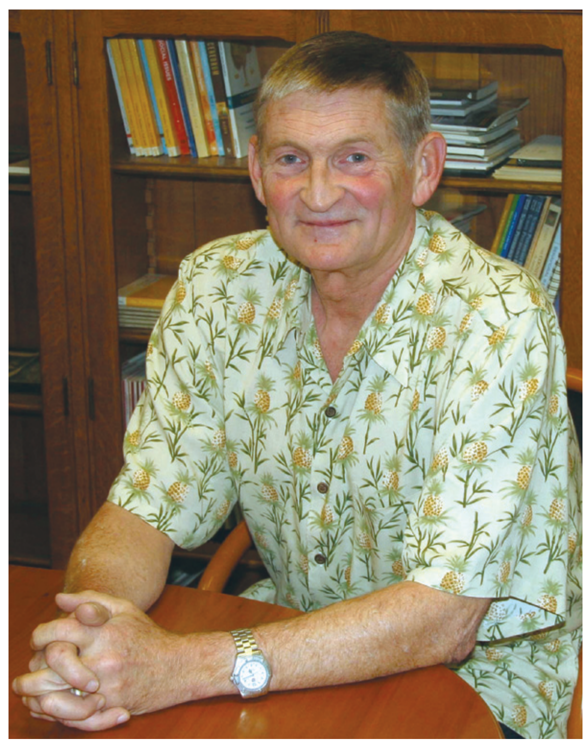
Their preliminary results show that ECoG could be used to control language and simple motor actions. In some tasks, for instance, patients are instructed to discriminate amongst auditory and speech sounds; they are able to use their thoughts alone to select a "beep" instead of a "boop", or "pa" instead of "ba"—building blocks of language. Eventually, patients may be able to choose sequences of these building blocks, allowing them to form words and sentences—all through simple imagination.

To demonstrate how brain signals can control neuroprosthetics, Knight holds up a water bottle in front of me. "Take a good look at this, and then close your eyes. Can you see the water bottle in your head?" he asks. Then he waves his hand back and forth in the air and instructs me to do the same. "Now close your eyes and imagine that you're moving your hand the same way. Can you imagine your hand moving?" I certainly could.

"The same brain regions are activated when you see or do something and when you imagine seeing or doing the same thing," says Knight. In order to construct BMIs that can mimic complex movements in natural settings, Knight believes it will be crucial to first gain a thorough understanding of how the brain generates signals that control movement.

"It's a baby field with lots of promise. The challenge is to understand the motor-control signals better and to make a wireless device that will translate these signals into complicated 3D actions, like controlling a wheelchair, feeding oneself, and grabbing objects," says Knight.

To investigate these movement signals further, Knight is collaborating with BMI expert Jose Carmena, assistant professor in electrical engineering and computer sciences, cognitive science and neuroscience,



PEG SKORPINSKI

Professor Robert Knight would like to develop a world-class neuroprosthetic program at UC Berkeley and UC San Francisco, with the goal of restoring language and motor functions to paralyzed patients.

and according to Knight, "the guiding light in the operation."

BMI breakthroughs at UC Berkeley

Across campus, Carmena is making important new discoveries about how the brain orchestrates movement. In a paper that was published in *PLoS Biology* in July, he demonstrated that the brain can develop a motor memory for prosthetic control. That is, it is possible to train neurons in motor cortex to gain stable control of a prosthetic device, and, most importantly, these neurons are able to retain this knowledge day after day.

"We showed that long-term use of a neuroprosthetic device is associated with the formation of a mental representation of prosthetic function that is stable across time, readily recalled and resistant to unlearning," says Carmena.

Typically in BMI studies, scientists first record from a set of neurons while subjects perform predetermined movements, such as moving a hand towards circles on a screen in front of them. They then correlate activity from these neurons with specific movement elements, like hand velocity and the relative positions of the hand, elbow and shoulder. These statistical relationships help them construct a decoder that translates neural signals into movements of a robotic arm, or movements of a cursor on a computer screen. Finally, they put the decoder to the test: subjects must use their thoughts alone to control a robot's or cursor's movements. Based on information collected during the recordings performed earlier that day, the decoder takes the neural activity and translates it into movements of the robotic arm or cursor on a computer screen.

Unfortunately, because of tiny movements in electrode position, it has been challenging to guarantee that recordings come from exactly the same neurons every day, so decoders must be retrained before every session. In his latest study, however, Carmena took great care to ensure that he was recording from the same neurons every time. He found that these neurons were quickly able to remember how to control the BMI each morning. The neurons formed a stable activation pattern to control a cursor's movements toward targets on a computer screen.

Once neurons settled on this pattern, Carmena decided to scramble the decoder into a nearly random translation. That is, he took each neuron's activity and translated it into a random arm position, unrelated to the arm position that the neuron originally encoded. Amazingly, he found that these same neurons were able to figure out the new "code" for controlling the computer cursor within just a few sessions.

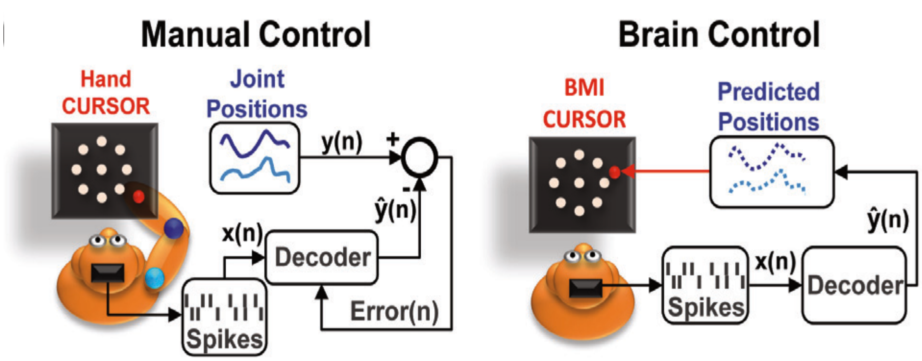
In addition to demonstrating the brain's impressive plasticity, Carmena's study yielded other valuable insights. He reintroduced the original decoder (decoder A) to the same neurons to see if they still remembered the original code, and he found that they did. "A small set of neurons could hold on to many different motor memories," says Karunesh Ganguly, a postdoctoral fellow in the Carmena lab and first author of the *PLoS Biology* paper.

Scientists at other institutions are taking notice. "Carmena clearly demonstrated for the first time that if you can record the same neurons over many days, you could then track how they learn different motor skills and readily switch between them," says John Kalaska, professor of physiology at the University of Montreal. The same small number of neurons were able to perform multiple tasks: they were able to learn decoder A, retain that skill, learn decoder B, and then switch back to decoder A. "Neurons are not locked into certain patterns," he adds. The results show that the brain can use many different solutions to solve problems.

Kalaska, an expert on motor control and motor learning, likens these findings to prism adaptation experiments. When human subjects first put on a pair of prism glasses that shift their entire visual field, they cannot accurately reach out and grab an object, like a cup of coffee. Initially, their arms reach out in the opposite direction, to a degree that depends on how much the glasses distort their visual field. Over time, however, they learn to adjust their arm movements when wearing the glasses—that is, they learn the new code or translation—and eventually they can accurately pick up a cup of coffee. Similarly, when the glasses are suddenly removed, they initially reach in the wrong direction before finally relearning the correct motor code.

In essence, Carmena showed that a similar type of motor learning can be accomplished very quickly by a small number of neurons in motor cortex, and that this motor learning can be used to gain impressive control over BMIs. "This is pioneering work that demonstrates how new technology can provide insights into fundamental issues of how the brain works, separate from helping paralyzed people," says Kalaska.

But the impact for patients cannot be overstated. These findings support the idea that the same neurons could learn to execute many tasks using a variety of neuroprosthetic devices. "This would greatly improve paralyzed patients' quality of life and ability to live independently," says Kalaska.



A schematic depicting how brain-machine interfaces work. Scientists record brain activity of subjects reaching toward circles on a screen in front of them. They then correlate neural activity with elbow and shoulder positions to develop a decoder, which later translates neural signals into movements of a computer cursor based on brain signals alone.

JOSE CARMENA

Moving naturally with BMIs

Across the bay, Carmena's latest discoveries elicit enthusiasm from a long-time friend and fellow BMI expert Krishna Shenoy, associate professor of electrical engineering, bioengineering, and neurosciences at Stanford University. Shenoy congratulates Carmena on "very innovative thinking and hugely important explorations of what the brain is capable of doing."

From a clinical perspective, Shenoy agrees with Knight that the best performance could be achieved by BMIs that mimic normal brain behavior. Shenoy likens it to learning a foreign language. You could try to teach someone a random foreign language, and they will eventually learn some of it. Or you could first ask them which languages they already know, and then pick a foreign language that is most similar to those. When starting from a more familiar language, they would immediately begin to perform better.

"Imagine that you go into a 7-11 and want to press the Coke button, not the Pepsi button, or swing a bat, or pick up your kids. Many neuroscientists believe that this kind of precise control can only be achieved through activation of the brain's natural patterns. The biggest challenge is to understand enough about how the brain actually works under natural conditions," he says.

Carmena admits that it may be challenging to build a BMI that responds and adapts to events in the environment strictly by mimicking natural brain patterns. "When you 'close the loop', or provide environmental feedback to the BMI, you are changing the inputs to the brain, and as a result, changing motor responses. It's very difficult to keep the same patterns of brain activity under these conditions," he says.

However, he and his students are exploring new ways of optimizing BMI performance under natural conditions. "A standard problem in the field is to design a BMI that can grab a glass of wine," says Carmena. To pick up a glass of wine without dropping it, crushing it, or missing it entirely, you need to have precise sensory feedback from multiple channels, such as touch, vision and proprioception, which is used to keep track of your body's movements and positions. "We plan on stimulating neurons in sensory parts of the brain to mimic natural feedback from many sensory modalities," says Carmena.

Slip-sensors, for instance, could be used to detect when the wine glass is slipping and trigger a robotic hand to squeeze tighter. "Although it is possible to design a robot that does this automatically, we believe you can get better control by using the brain," says Subramanian Venkatraman, an electrical engineering graduate student in the Carmena lab. His latest research shows that microstimulation can actually evoke a sensation similar to natural touch. However, he quickly points out that it is not necessary to exactly mimic natural sensation to get accurate control with BMIs. "You could learn to use sensory feedback from microstimulation even if you don't stimulate the precise neural circuitry that's naturally involved; it would just feel a little artificial," says Venkatraman.

Professor Jose Carmena recently discovered that brain cells can quickly form a stable motor memory to control prosthetic devices.

The future of BMIs

It's not likely that patients will be using BMIs to pick up wine glasses anytime soon. Currently, the risks from surgery and unreliable electrodes outweigh the benefits, except for three types of patients: those with damage to the high cervical part of the spinal cord, which causes quadriplegia; those with Amyotrophic Lateral Sclerosis (Lou Gehrig's disease), a neurodegenerative disorder that causes motor neurons to die and later leads to complete paralysis; and those with "locked-in syndrome," a condition, typically caused by a stroke in the brainstem, that causes patients to lose control over all muscles except for the eyes. To increase BMIs' potential benefit to a wider spectrum of patients, it will be necessary to improve the performance of BMIs, decrease their invasiveness, or both.

University of California scientists are on the path to achieving this goal and eventually restoring language and motor functions to paralyzed patients. Knight is committed to developing a joint, world-class neuroprosthetic program with UC San Francisco (UCSF), in collaboration with two neurosurgeons who have been instrumental in his experiments: Mitchel Berger, neurosurgeon and chair of neurological surgery at UCSF, and Nicholas Barbaro, neurosurgeon and co-director of the Functional Neurosurgery Program at UCSF. "We've received supportive feedback from deans on campus, but what we really need now are some large donations to help jumpstart the center," says Knight.

Although ubiquitous neuroprosthetics may seem like a farfetched fantasy at the moment, Carmena and Knight expect they will follow the same successful path as previous cutting-edge medical implants. "In the 1970s, defibrillators were an experimental treatment for cardiac arrhythmia; now they're widely used. In the mid-1980s, cochlear implants were approved by the FDA to restore hearing. More recently, deep brain stimulators were introduced as an experimental treatment for Parkinson's disease and other neurological disorders. All of these were once crazy ideas that are now accepted, because they work," says Knight.

In the meantime, debates about the most promising approaches—invasive or noninvasive, or those that mimic or bypass natural circuitry—continue to rage on. "Scientists are working in parallel to accelerate discoveries in the field," says Carmena. Shenoy agrees that the multifaceted approach is optimal. "Show me a medical technology where it's not better to have more options," he says. One day, patients may be able to walk into a clinic and choose from a suite of BMI options that cater to their individual needs.

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