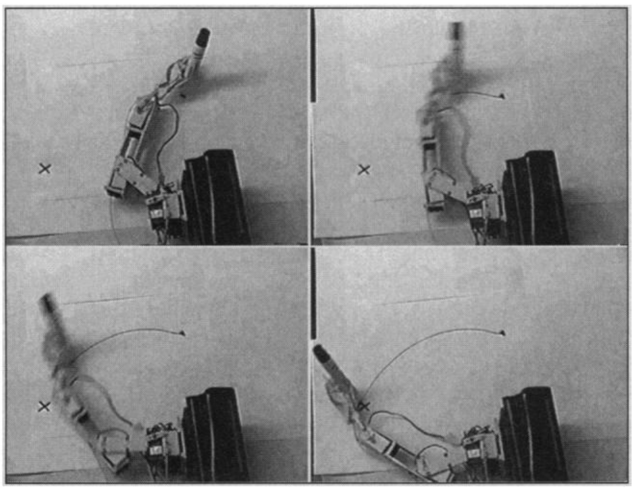
A flurry of new work suggests that paralysis victims could soon benefit from devices that translate their thoughts into commands to operate computers or even robot limbs

Turning Thoughts Into Actions

Performing a task any healthy rodent can master, a rat in a video depresses a bar in its cage to get a metal arm to swing inside and deliver a sip of water. The next time around, the arm swings early—before the rat has even finished pressing down. "Do you see the surprise in his eyes?" jokes neuroscientist John Chapin of Hahnemann University in Philadelphia, knowing full well that those beady black orbs don't betray that emotion. However, this is not a prank some character in a "Far Side" cartoon might pull. The water arrived a fraction of a second early because the arm was driven by neurons in the rat's brain that signaled its intention to press the bar with its paw.

Chapin's rats are test subjects for pioneering machines that can translate thoughts into action without the need to twitch a muscle. The ultimate beneficiaries of these now-primitive devices could be millions of quadriplegics and the half-million or more patients worldwide who are "locked in"—so utterly paralyzed that some are unable even to blink. A tool that could read their thoughts to execute commands or compose letters on a computer, for instance, would become a lifeline to the outside world. For many, such a modicum of independence may offer a reason to live.

"These people have nothing," says neuroscientist Emanuel Donchin of the University of Illinois, Urbana-Champaign, of the locked-in patients he hopes to help. "A lot are allowed to die," he notes, and some, who gradually become locked in through progressive diseases such as amyotrophic lateral sclerosis (ALS), may choose to end their lives. "[If] you could offer them some minimal quality of life, they might choose to [live]."



Using its noggin. In this experiment, John Donoghue's team tapped a monkey's thought patterns to drive a robotic arm holding a pen. More graceful movements may simply require listening to more neurons.

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Only a few years ago, thought-driven machines were the stuff of science fiction, not science. But the field of neuroprosthetic devices is advancing quickly, spurred by an influx of talented researchers who say the brain may be more primed than anyone had realized to learn to treat a cursor or a robotic arm as an extension of the self. A first generation of communication devices, driven by brain waves detected from outside the body or by electrodes implanted in the brain, is now being tested in paralyzed patients. And recent research, some of it presented earlier this week in Miami at the annual meeting of the Society for Neuroscience, suggests that more sophisticated devices allowing people to operate a robotic arm by thought alone may not be far behind.

Many technical hurdles remain, including the need for longer lasting electrode arrays that are more compatible with brain tissue and the puzzle of how to make robotic limbs move and respond in the most realistic manner. But such obstacles don't seem insurmountable, experts say. "A lot of these things are engineering problems, not scientific problems, and they will be solved," says neuroscientist Andrew Schwartz of the Neurosciences Institute in La Jolla, California, who is collaborating with an engineering team at Arizona State University to develop a prosthetic arm.

Work on prosthetic devices that tap directly into the nervous system has been going on for years and already has a great success story: cochlear implants that stimulate the auditory nerve, which are now widely used to restore hearing to deaf patients. Then, in the 1980s, a band of researchers began devising techniques for making information flow the other way—wiretapping the brain's internal communications.

Some chose to develop devices that could be steered by brain waves detected outside the head; research more than 30 years ago showed that people can be trained to control these patterns. Another group of researchers was inspired by findings on how populations of neurons in the brain's motor regions work together to encode the direction of limb movements, advances led by neuroscientist Apostolos Georgopoulos of The Johns Hopkins University School of Medicine. Those discoveries, as well as the advent of electrodes that could record from dozens of neurons at once, raised the possibility that one could tap those "population codes" to drive prosthetic limbs.

The first patients to benefit from brain-driven prostheses are likely to be people with locked-in syndrome. Stricken with advanced ALS, brainstem strokes, or traumatic injuries, they are totally paralyzed, their breathing controlled by ventilators. For the fraction of locked-in individuals who can move their eyes, computer setups can track eye movements and allow the patients to spell out words by looking at letters on a screen. But the most severely locked in do not have reliable control of their eyes.

It is for those patients that researchers such as Neils Birbaumer of the University of Tübingen, Germany, and Jonathan Wolpaw of the New York State Department of Health's Wadsworth Center in Albany are working. They set out more than a decade ago to harness for communication the ability of people to control their electroencephalograms (EEGs), the patterns of brain waves detectable by electrodes placed on the scalp. The EEG is the sound of the brain at work, an electrical hum escaping from the skull that reflects the overall activity of neurons firing in the cerebral cortex.

The two teams have used similar strategies: linking EEG patterns to the movement of a cursor on a computer screen, then training subjects to control cursor movements by altering their EEGs. Birbaumer's team focused on a particular EEG readout called the slow wave, which reflects the overall negative or positive charge of the EEG pattern. They taught patients to control the wave by playing a simple game: "On the computer you see the negativity in the form of a light ball which moves across the screen toward a goal," he says. "If it reaches high enough amplitude, the goal lights up." Because the EEG measures the average of many types of brain activity, it's hard to instruct patients on how to control it; they must learn through trial and error.

Wolpaw prefers to use the "mu" wave, which emanates from the scalp near areas in the cortex that control movement. He says his subjects often begin learning to control it by imagining themselves playing a sport. "Eventually," he says, "they say they don't need the imagery anymore." He has found that healthy subjects can gain control of a cursor within 10 sessions and thereafter become faster and more accurate. The subjects can answer four yes-or-no questions in a minute, about a quarter of the speed it would take to say the answers.

Birbaumer's team, meanwhile, built a device that lets people use a cursor to spell out words. The subjects answer yes-or-no questions to indicate which half of a progressively divided alphabet contains the letter they want. The team has so far trained three locked-in patients to use the device. The pace is slow—two or three letters per minute at best—and can be exhausting, says Birbaumer. But, he adds, his patients are so glad to be able to communicate that they "don't care about speed at all."

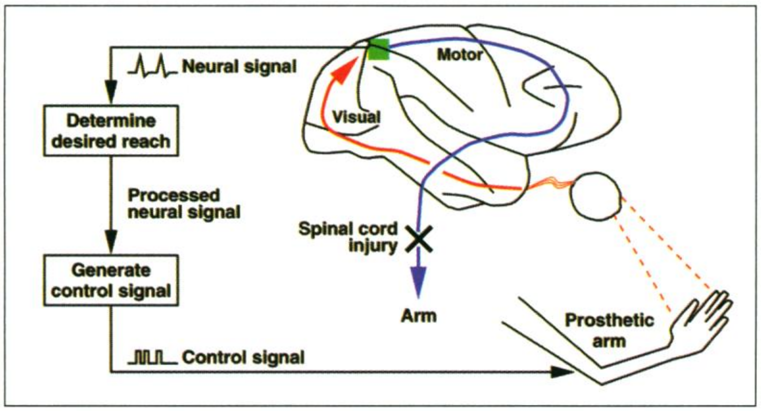
Despite the appeal of this noninvasive technique, most researchers agree that EEG patterns cannot convey enough information to generate the complex and rapid commands necessary to move a prosthetic limb. "That will never happen," says Birbaumer. But that mountain may be climbed with another class of neuroprostheses, in which neural signals are gathered directly via electrodes implanted in the brain.

The first of this breed has just made its debut in human beings. Philip Kennedy, chief scientist of Neural Signals Inc. in Atlanta, Georgia, has built an electrode that releases a cocktail of growth-promoting compounds. The biochemicals coax neurons to sprout projections that grow into the electrode's porous tip, where it registers their activity. In 1996, Kennedy received approval from the Food and Drug Administration to test the electrode in humans; his collaborator, neurosurgeon Ray Bakay, has so far implanted it in three locked-in patients.

Because his goal was to have patients use their neural activity to move things—first a cursor on a computer screen and someday a prosthetic arm—Bakay placed the electrode in a brain area involved in controlling movement, the primary motor cortex. He used functional magnetic resonance imaging to visualize brain activity while the patients imagined moving a hand. Next, he inserted the electrode in the brain region active during the test.

One patient died from her disease shortly after surgery, while another had the procedure in July and is waiting for the neurons to finish growing into the electrode. But the third, a 53-year-old man paralyzed by a brainstem stroke, has had the electrode for more than a year, and he has learned to direct a cursor to choose letters and spell messages. First the man succeeded by thinking about moving his hand, says Kennedy, but now he simply thinks about the cursor itself to make it move.

That testifies to the brain's remarkable plasticity, Kennedy says. Scientists have known for years that unused portions of the higher brain can take on new functions—for example, the visual cortex of a blind person can register the tactile sensations for reading Braille—or that a neighboring brain area can take over the functions of one destroyed by a stroke. In Kennedy's patient, it appears that the brain area once devoted to moving the patient's now-paralyzed hand has adjusted to its new-found ability to move the cursor, evolving into what Kennedy calls a "cursor-related cortex." Such adaptability will be the key to success for future devices, says Kennedy, adding that "Plasticity is our friend."



The elbow's connected to the cortex. Say you want to grab a piece of candy. Your visual system (red) sends information to the posterior parietal cortex (green), which plans the movement and sends commands to the motor areas (blue). The motor cortex elaborates these plans into precise instructions sent via the spinal cord to the arm muscles—signals that get derailed in paralyzed patients. Several research groups are devising methods to use intercepted brain signals to operate a prosthetic arm, thus bypassing a damaged spinal cord.

CREDIT: R. ANDERSEN

However, the device has been tested only in a single patient so far. And although Kennedy and others believe that direct recording from neurons will eventually prove superior to EEG-driven devices, they have a long way to go before the benefits of implanting them into a lot of patients outweigh the risks of surgery. Birbaumer's EEG patients "can do three letters a minute, and on a good day [my patient] can do better than that," says Kennedy. "But he can't do 10 times better."

Getting brain neurons to drive prosthetic limbs will require electrodes, now under development, that can tap more than just a handful of neurons. "If the technology can generalize to … recording from 100 or 200 [neurons], that is when you are going to see a major step forward," says William Heetderks, director of the Neural Prosthesis Program at the National Institute of Neurological Disorders and Stroke in Bethesda, Maryland.

Indeed, a tide of neuroscientists surging into prosthesis research got involved through a quest to understand how the brain encodes information. Their approach is to analyze electrical patterns recorded from dozens of neurons at once (*Science*, 17 April 1998, p. 376). "We were interested in this for mainly theoretical reasons," says Chapin. "The issue is how the brain works, and neural population coding is the essence of that problem. Then, the idea of solving a practical problem, which is neural prostheses, came along."

Chapin's team at Hahnemann wanted its rats to perform a task requiring a specific force of paw pressure, and precise timing, to see if the code for those elements could be deciphered from the animals' neural activity and translated into moving a mechanical arm. The team members devised a task in which a spring-loaded bar controlled a swinging arm with a cup at the end. A rat had to push the bar down just far enough to swing the arm until the cup was under a stream of dripping water outside the cage, hold the cup there to catch some drops, then release the lever, allowing the arm to return so they could drink.

In the region of the rat's motor cortex that controls paw movement, the team implanted an array of 24 microelectrodes that could record the firings of up to 48 neurons at once. "We found that the activity in the brain just before the animal pressed the lever carried a code for how far down the lever would be pressed," says Chapin. The team fed the neural firing pattern into a computer that would translate it into a signal to move the arm the right distance. Then "in the middle of the experiment, we switched the switch, and suddenly the robot arm was being controlled from the brain," Chapin says. "The question was: Can the animal still move the robot arm to the water? The answer was that he could."

Chapin's team, with collaborators led by Miguel Nicolelis at Duke University, is trying to repeat its success in monkeys, whose brains more closely resemble our own. Several others are also in the race. Groups led by John Donoghue at Brown University and Schwartz at the Neurosciences Institute in La Jolla are experimenting with multiple electrodes placed in the motor cortex of monkeys. And at the neuroscience meeting this week, Richard Andersen's group at the California Institute of Technology in Pasadena described similar experiments in the parietal cortex, which helps transform sensory information into plans for movements.

Brain bug. Several teams use this 25-electrode array (4.2 mm^2), seen next to a dime, to record neural signals from a monkey's cerebral cortex.

They all share the same goal: to use neural firing information recorded in real time to reconstruct the motions of the monkeys' arms. If the scientists can interpret the direction, speed, and distance of arm movement from the corresponding neural signals, then they should be able to use the nerve-firing pattern to direct the movements of a mechanical arm.

The hope is to "generate natural-looking arm movements, like reaching toward a glass, or gesturing," says Schwartz. Toward that goal, Matt Fellows and Liam Paninsky from Donoghue's team also reported at the meeting that they have recorded neuron firing in the motor cortex as a monkey used its hand to follow a randomly wandering cursor across a screen. From the firing patterns, the researchers derived a mathematical code that could reconstruct the path of arbitrary arm movements the monkey made later.

That all these variables could be predicted "based on the information you can get out of fewer than a couple of dozen cells," Donoghue says, "means the potential for recreating the entirety of any movement is much better than I would have expected." His team has already used neural information recorded from a monkey to direct the movement of a prosthetic arm to one of eight points in space, and it plans to go on to more natural, less constrained movements.

Schwartz and his collaborators at Arizona State have just achieved that goal. At a neural prosthesis workshop at the National Institutes of Health 2 weeks ago, Schwartz reported that they have operated a robotic arm directly from recordings of 26 neurons in a monkey's brain, mirroring the animal's own arm as it pushed buttons on a panel or chased an almond across a tabletop. The neural activity provided velocity and direction of movement, which the researchers fed every 20 milliseconds into the computer controlling the robot. The computer determined which joints to move, and how much. The result, says Schwartz, is "three-dimensional, natural arm movement through free space."

In these experiments, the monkeys went about their business unaware of the robotic arm. The next step will be to have the animals consciously controlling the arm, much as a paralyzed person might.

The eventual performance of these devices in people will be aided, researchers expect, by the brain's well-proven plasticity in adapting to new tasks. That plasticity suggests that implantable prostheses need to be placed only in the general vicinity of the correct brain region—such as the motor cortex—rather than linked up to the very neurons devoted to particular movements, a correspondence that may be impossible to achieve in paralyzed patients. Then the brain should take over, learning to run the prosthesis with whatever neurons have been linked to it, much as neighboring brain areas assume new tasks after a stroke.

Another hurdle to surmount is how to incorporate sensory feedback, such as pressure from touching an object, into a prosthesis. However, robotics research has shown that people get "an amazing amount" of useful feedback solely from what they are seeing, says Schwartz, who believes this will not be difficult to overcome. A stickier problem, he says, will be getting enough neural information to control fine hand motions. But even movements crude enough to grasp a spoon could make a big difference in a paralyzed patient's life. "If they could feed themselves, that would be huge," Schwartz says.

Scientists are optimistic that the engineering will carry the day, now that neuroscience has shown that the brain has the potential to control prostheses directly. If so, these scientific advances could soon be transformed into improvements in the lives of paralysis victims. "In principle, it should all be possible," says neuroscientist Eberhard Fetz of the University of Washington, Seattle. "The question is to what degree it will become practical." But with the new surge in interest and funding, Chapin predicts that goals "that looked like they might be 15 to 20 years off will suddenly be 5 to 10 years off."

–MARCIA BARINAGA

ARCHAEOLOGY

A Long Season Puts Çatalhöyük in Context

A marathon dig at one of the world's most famous Neolithic villages links it to other, older Near Eastern settlements

ÇATALHÖYÜK, TURKEY—Archaeologist Mirjana Stevanovic is still wondering about the skulls. Last summer, while excavating at this 9500-year-old Neolithic village near the modern city of Konya, Stevanovic and colleagues from the University of California (UC), Berkeley, found two skulls—with no skeletons attached—in a large house. One was that of a boy about 12 years old; the other belonged to a woman in her late 20s. They had been placed on the floor with their foreheads touching. The skulls were discovered very near the spot where, in 1998, the team found evidence that the roof had collapsed.

Did the woman and boy die in the cave-in? Were they mother and child? Both skulls have unusual suture patterns in their bones, possibly lending support to the notion that they were related, says Başak Boz, an independent anthropologist from Ankara who is working with the team. And other clues at the site suggest that family ties were very important to these villagers.

But no one can say for sure why the skulls were placed together. "All I know," says Stevanovic, "is that they were put that way deliberately."

The skulls are just one more puzzle at Çatalhöyük, the largest Neolithic community yet discovered, which offers a rare glimpse of early settled life. But, although the secret of the skulls may never be revealed, the international team that has been excavating here for the past 6 years is beginning to decipher other mysteries of this ancient settlement. A

Neolithic neighbors. Çatalhöyük is now seen as part of the same cultural tradition as other ancient Near East villages.

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