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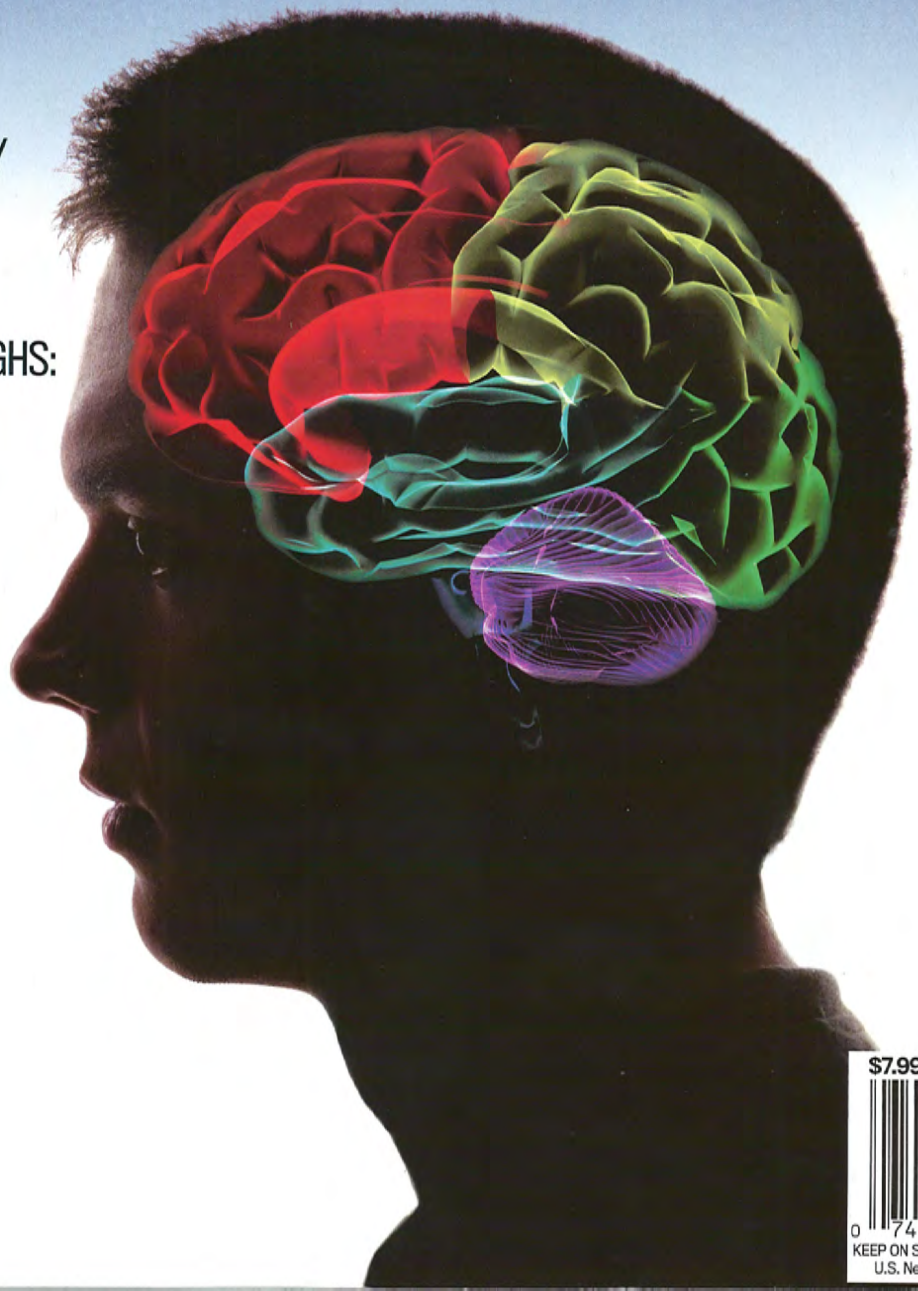

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U.S. News Special Edition, Volume 2

Three Patients, Three Operations

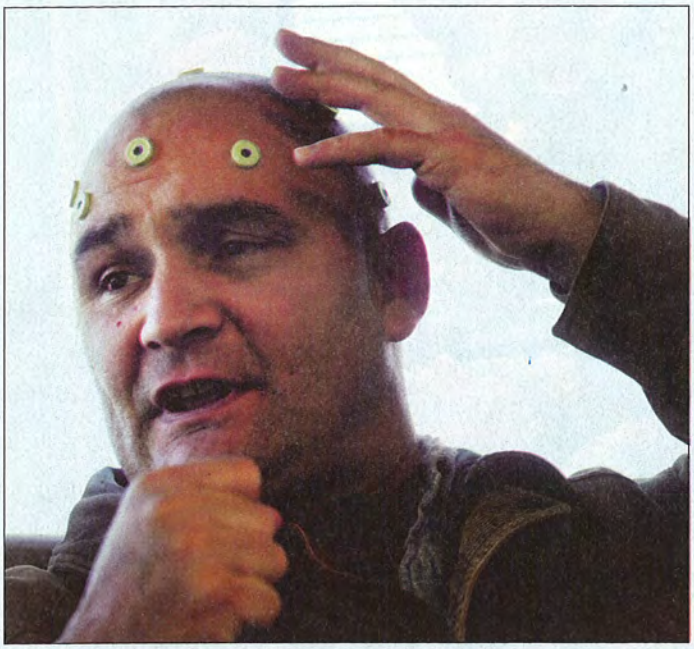
TAKE A FRONT-ROW SEAT IN NEUROSURGERY AT THE UCSF MEDICAL CENTER

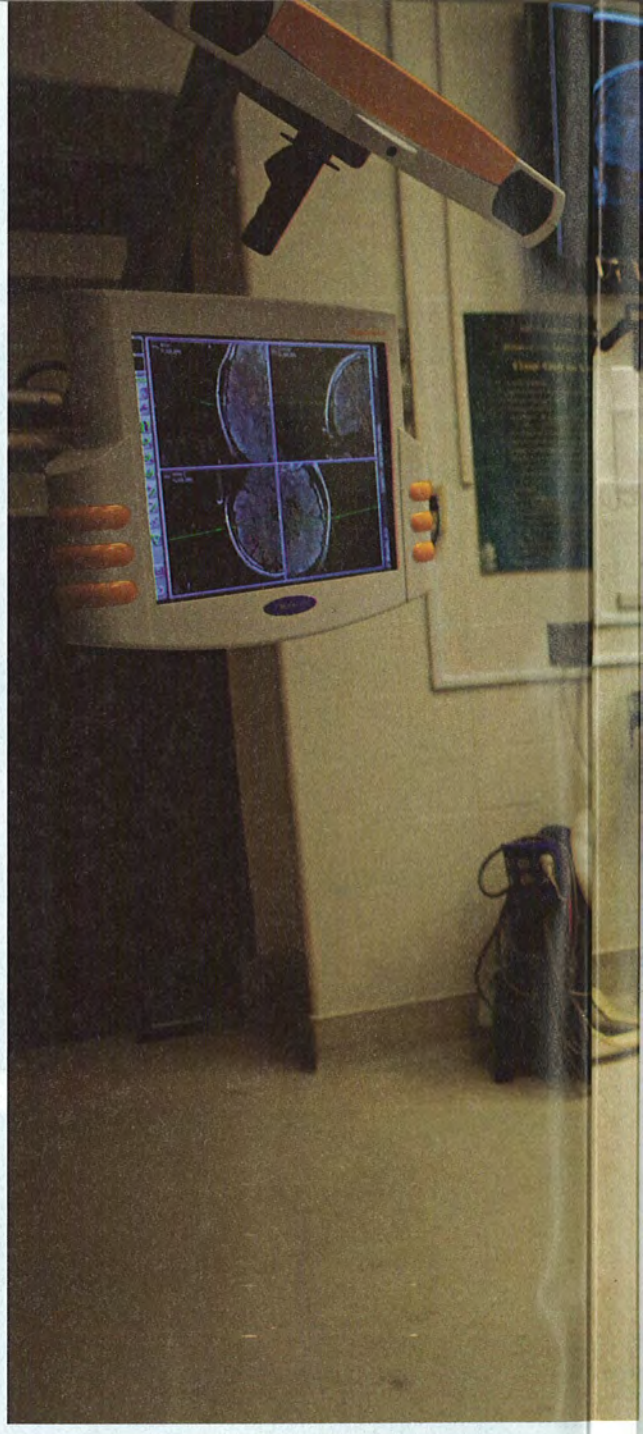
SAN FRANCISCO—If a person suffering from the tremors and rigidity of Parkinson's disease chooses brain surgery, she will most likely need to go off her medications and be awake during the procedure so doctors can gauge her ability to speak and move as they maneuver. That's been the uncomfortable reality for people who have experienced deep brain stimulation, a state-of-the-art technique that implants electrodes to calm erratic nerve signals and ease symptoms. But at the University of California, San Francisco Medical Center, she has an even more cutting-edge option: She can stay on the meds and sleep through the operation inside an MRI machine while surgeons drill into her skull and use imaging to guide the electrodes safely into place.

This groundbreaking approach to deep brain stimulation (DBS), pioneered here and headed soon to the Cleveland Clinic, is one of the many examples of envelope-pushing going on at UCSF. The medical center, No. 5 in neurology and neurosurgery in the latest *U.S. News* Best Hospitals ranking, performed 3,479 neurosurgeries last year. While most are fairly standard fare, such as removing benign tumors and easing seizures, people from around the world come here to put their brains and their hopes in the hands of surgeons testing medical frontiers. One is using a dye

Photography by Daryl Peveto-Luceo for *USN&WR*

Parkinson's patient Linda Sharp (top left) chose deep brain stimulation using interventional MRI, allowing her to sleep through it. As the MRI room was being prepped as an OR (opposite bottom), surgeon Philip Starr readied her for surgery (above), which involved drilling into her skull and using imaging to thread electrodes into place (at left).





After Daniel Sheafer (pre-surgery, top) had his tumor removed, surgeon Edward Chang gave fiancee Gina Meldrum (bottom) the good news.

that makes even single malignant cells glow orange under fluorescent light so it's possible to better target them for extraction. Another research project, also in the Parkinson's realm, is investigating the potential of infusing corrected copies of defective genes into the brain; clinical trials could begin as early as this year. One surgeon is mapping electrical activity when a person who is undergoing "awake-brain" surgery speaks; the goal is to create a voice prosthetic for people who can't talk. *U.S. News* recently spent two days at UCSF to watch the neurosurgeons in action.

An MRI room isn't normally set up for surgery, but the imaging center has been transformed today into a bona fide operating room. By readying a set of non-magnetic titanium instruments (so the giant magnets at the core of the imaging system don't tug them out of the surgeon's hands) and draping sterile sheets around the opening of the MRI tunnel, the surgical team has prepared the suite for Linda Sharp's deep brain stimulation on this chilly San Francisco morning in January.

Sharp, 71, began her journey here about 12 years ago, when her left leg began to fail during walks to her gym in Los Osos, Calif. In 2001, she was diagnosed with Parkinson's and subsequently developed dyskinesia, which produces uncontrollable bouncy movements in her legs. Meanwhile, neurosurgeon Philip Starr was brainstorming a

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better way to implant electrodes for DBS. About 50,000 Americans are diagnosed with Parkinson's each year, he says, and about 10 percent of them could benefit from the stimulation. But many are not good candidates for awake-brain surgery because they're too nervous or experience involuntary movements. Taking advantage of the rapidly advancing quality of MRI images, Starr, fellow surgeon Paul Larson, and MRI physicist Alastair Martin developed an "interventional MRI" procedure that allows them to see deep inside the brain as they operate and the patient sleeps. Collaborating with SurgiVision, a Memphis-based company that develops MRI software and hardware to guide electrodes into the brain, the team received Food and Drug Administration approval last July for the new iMRI system. (Elsewhere, MRI-guided surgeries are being tested or used to accurately point a laser or high-intensity focused ultrasound at some tumors and uterine fibroids.)

On this morning, Sharp was positioned inside the MRI scanner to capture a pre-surgery image that would determine the safest trajectory for the electrodes, plastic-encased wires as flexible as partially cooked spaghetti. The surgeons then drilled two nickel-sized burr holes in her skull and affixed a plastic frame that would allow them to precisely thread the electrodes, by turning knobs to tweak the angle of entry, into each hemisphere's subthalamic nucleus, the problem zone. Images were taken

Chang (above right) scanned the terrain before opening Sheafer's skull and waking him up to map (and thus avoid) areas key to speech and movement.

throughout the insertion to watch for hemorrhaging and to ensure that the electrodes hit the target.

The night before her operation, Sharp had admitted to feeling apprehensive; one of her friends had suffered speech problems following traditional DBS surgery. But after the roughly three-hour procedure, she came out of recovery smiling and with her speech intact. A week later, a second surgery threaded the ends of the electrodes, which had been coiled under Sharp's scalp for safekeeping, under the skin of her neck and connected them to a device placed under her collarbone that generates electrical pulses. The full benefits should be seen over the next six months, as the pulse is programmed to suit her and her meds are adjusted.

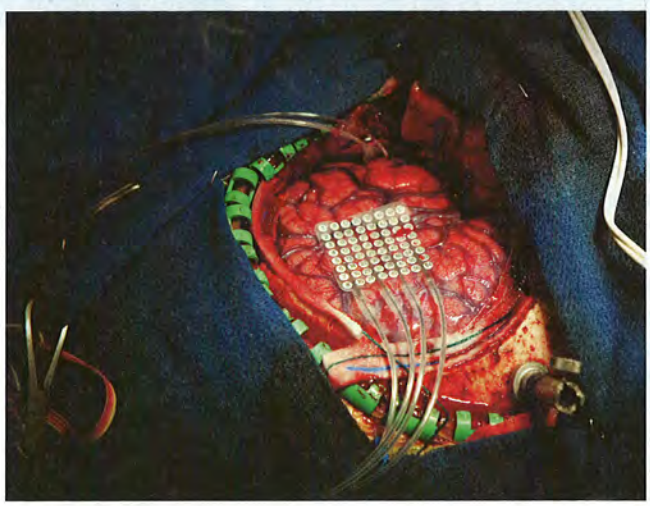
The day after Sharp's procedure, Daniel Sheafer's brain was exposed to the air in a standard operating room. Sheafer, 38, of Modesto, Calif., learned he had a tumor in his temporal lobe last year after painful headaches kept him from working his landscaping and other jobs. "It felt like a cue ball was bouncing from side to side in my head," he recalled at UCSF the day before his operation. The fact that Sheafer suffers from epilepsy complicated matters, says surgeon Edward Chang.

If the tumor were accessible, Chang planned to remove as much of it as he could (iMRI wouldn't be used; the procedure is approved specifically for DBS). He would also try to locate the source of Sheafer's seizures, in the hope of addressing it surgically. Finally, if Sheafer stayed calm during the awake-brain part of the procedure, Chang would take advantage of the patient's willingness to help out with his research: gathering data about the electrical activity that produces speech. Chang would apply sensors directly to Sheafer's temporal lobe to record the location of electrical bursts produced when he repeated certain words.

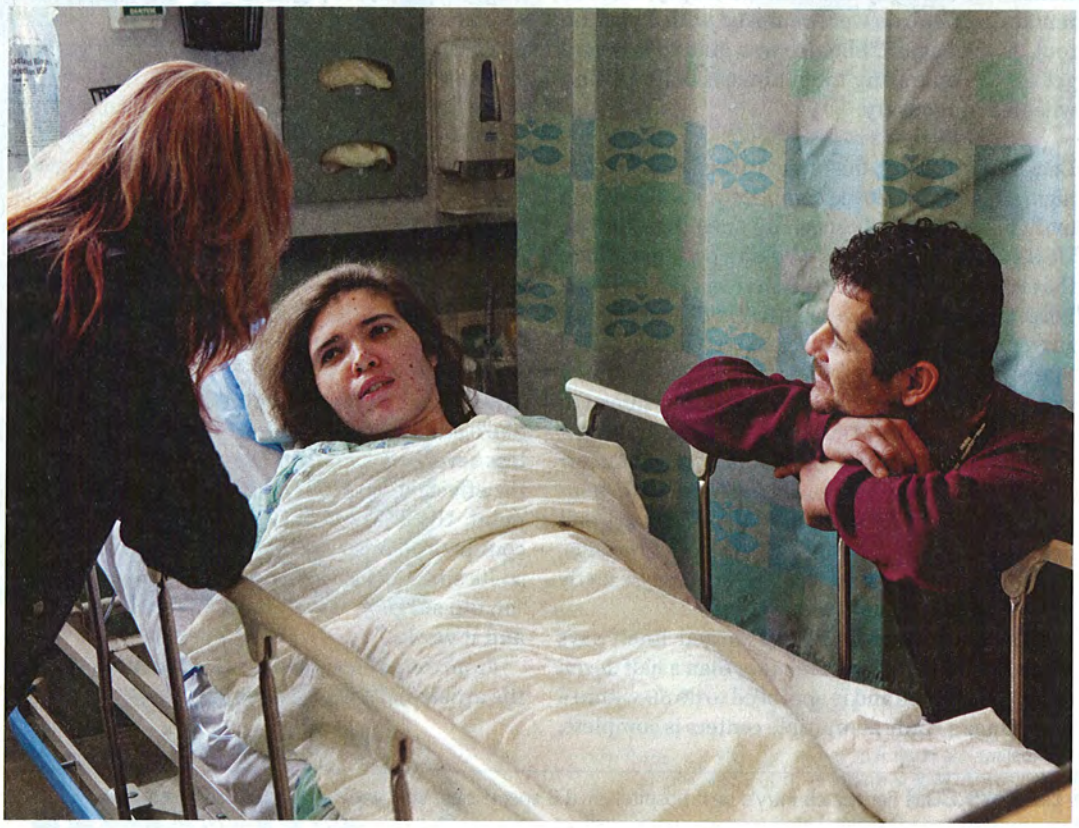
Chang has been performing these on-brain electroencephalograms, or EEGs, for two years, using the data to refine software algorithms that match electrical signals to sounds like "ba" and "da." The next step is to correlate the signals with sounds as a person thinks them. Eventually, Chang hopes, a device implanted on a person's brain will "read brain activity, do computations, and wirelessly output the information to a computer that decodes it and fits it into a speech synthesizer." Think it, and a computer will say it. While a voice prosthetic will likely take years to perfect, the first human trials should begin this year.

After Sheafer, a devout Christian, had led the team in a prayer, he was sedated so the surgeons could remove part of his skull. Then, to safely get at the wispy, wave-shaped tumor 3 centimeters beneath the surface, Chang needed his patient awake so he could map the parts of Sheafer's brain that control his movement and speech. The surgeon electrically stimulated Sheafer's cortex while asking him if and where he felt tingling sensations in his face. He also asked Sheafer to identify objects in pictures and to count. All the while, eight electrodes kept watch for seizure activity.

After mapping the brain for the tumor removal, Chang applied his speech sensors, and Sheafer repeated words from a list while electrical signals were recorded. On a computer monitor, a yellow line jittered as Sheafer's brain donated its language secrets to science.



Chang's work on a prosthetic to turn brain waves into speech got input from Sheafer, who spoke as sensors on his brain (right) monitored activity associated with sounds.



Before surgery (above), Savanna Kelley and her parents, Marisa Martin and Brian Kelley (at left), hoped that her corpus callosotomy would ease seizures so severe that they cause her to collapse. The operation severs many of the fibers connecting the brain hemispheres, disrupting signals between them.

Kelley's surgeon Chang (above right), operating with clinical fellow Ellen Air, estimates that 50 or so corpus callosotomies are performed in the country each year. While not a cure for epilepsy, the procedure alleviates most patients' "drop attacks."

With his brain mapped and data-gathering complete (no luck pinpointing the seizures), Sheafer was again sedated. Chang scooped out an inch-square chunk of lateral cortex, revealing the dark gray tumor below. A portion of the tumor was cut away and sent for biopsy, and the remaining tendrils were removed with a suction tool. Awake again, Sheafer was able to talk and get off the operating table himself before being wheeled to recovery.

Luckily for Sheafer, the tumor turned out to be benign, and it was removed completely. For those with malignant growths, especially ones that sprawl, UCSF Medical Center is working on a technique that could produce much better results. Mitchel Berger, chairman of the department of neurological surgery, is one of a handful of doctors in the United States with FDA approval to do the dye-activated visualization procedure, which has been shown to significantly improve survival. The patient drinks an organic dye called 5-ALA, which targets tumor cells by interacting with their overactive mitochondria. When the cancer cells metabolize the dye and are exposed to fluorescent light, they glow orange, indicating with unprecedented accuracy exactly what a surgeon should remove.

"It's like cutting along the dotted line," says Berger, who has completed more than a half dozen of the procedures and is approved to do 50 within a year. Once a study at multiple centers is complete, says Berger, there's a good chance that the procedure could be broadly approved by the FDA; he estimates this could happen in three to five years.

That afternoon, Chang was back in the OR with Savanna Kelley, a shy 23-year-old with epilepsy who was regularly experiencing grand mal seizures powerful enough to send her to the ground. Kelley, who is developmentally delayed, had recently started a vocational program near her hometown of Lemoore, Calif., but the "drop attacks" had been getting in her way. "She wants to do stuff by herself," says Marisa Martin, Savanna's mom. "It's frustrating for her."

Kelley's procedure, a corpus callosotomy, severs many of the fibers of the corpus callosum, which connects the brain's hemispheres and facilitates communication between them. Afterward, the firestorm that starts on the left side of Kelley's brain won't be able to spread to the other side. She'll still have seizures, says Chang, but they'll be less severe. It usually takes a few weeks to know the effect, he says, but most patients see improvement. UCSF Medical Center does several of the country's 50 or so corpus callosotomies each year, so its surgeons are considered old hands. This is "an old surgery," says Chang. "It's tried and true and it works."

From the patients' perspective, that doesn't make the artistry, or the outcome, any less dramatic. ●

By Kate Greene

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