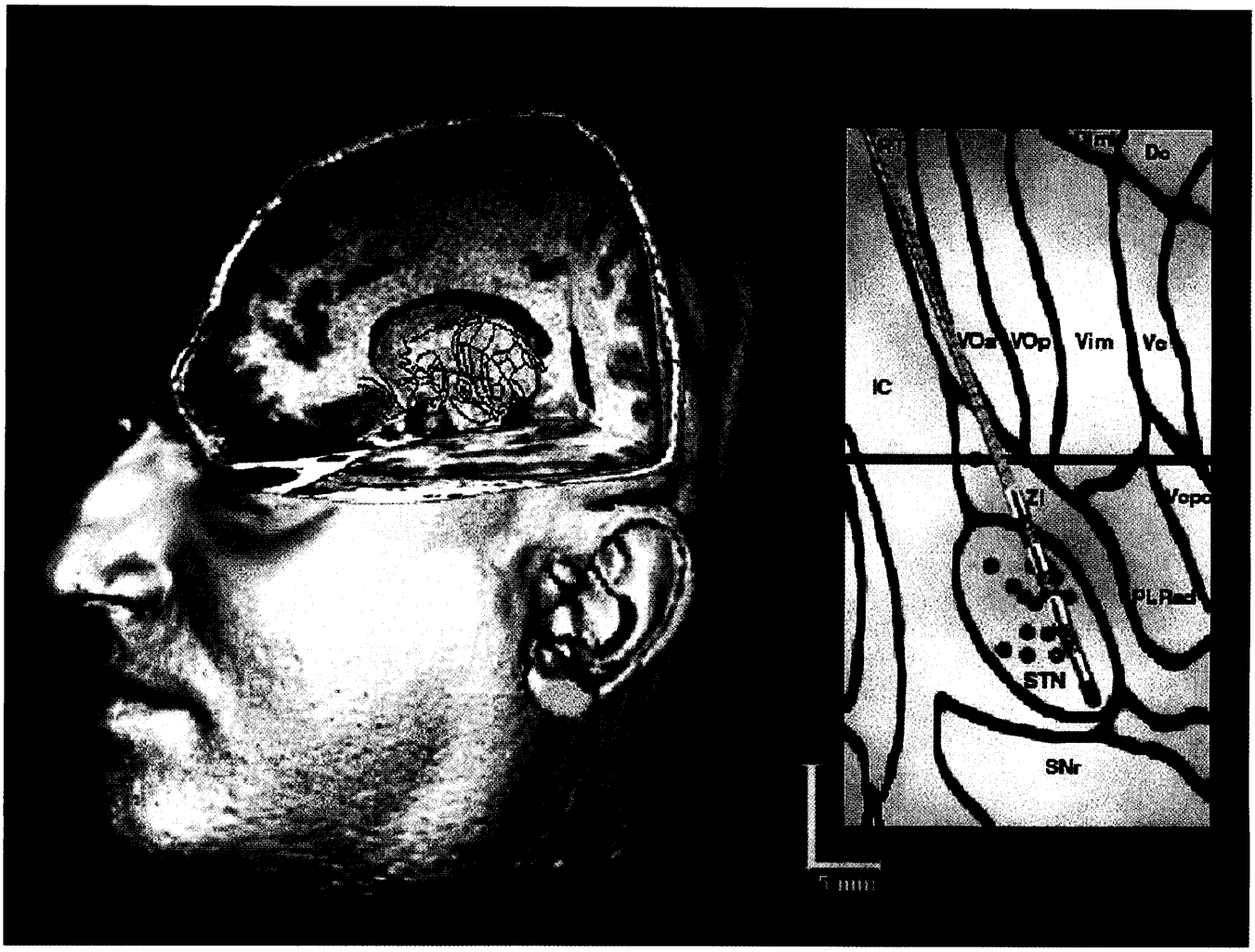

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Probing Minds

Brain scan: A 3-D reconstruction of an MRI image of the brain of a patient who has received deep-brain stimulation treatment for tremor caused by Parkinson's disease.

Cleveland neurosurgeons are pushing the boundaries of a new cerebral technology

By Anton Zuiker

Over the cackle of static, Abed Hammoud whispers to me through his surgical mask: "This is the frontier of medical technology."

Hammoud is not a surgeon. He has a Ph.D. in biomedical engineering and works for Medtronic Corporation. This snowy morning in December, he is in Operating Room Number Eleven at the Cleveland Clinic Foundation. He is operating the Silicon Graphics computer and Medtronic's software that is allowing Clinic neurosurgeons Ali Rezai and Erwin Montgomery to ever so slowly push an electrode the size of a hair deep into the brain of a man named Russell Purdue, in a procedure called deep brain stimulation (DBS).

DBS is a new surgical treatment for movement disorders such as Parkinson's disease, epilepsy and multiple sclerosis – all of which can cause immobilizing tremors in a person. ("It's as if you're driving with the parking brake on," says Rezai.) The Cleveland Clinic is the leading center for DBS in the United States.

Russell, a construction worker from West Virginia, has multiple sclerosis; his case is more difficult than the Parkinson's cases that Rezai has mastered, but the procedure is the same. The surgical team will find

the "sweet spot" in an area of the brain called the subthalamic nucleus that, when stimulated with the electrode, will shut down – stopping the tremors.

The peculiar noise filling the operating room, I learn, is not merely white noise to help the patient sleep – Russell is awake and responsive; it's actually the sound of Russell's brain.

What sounds like AM radio static mixed with Morse code are the conversations of neurons sending electrical signals back and forth. Montgomery eagerly follows this dialogue, for he's learned how to use the signals to help him pinpoint where in the brain the electrode is now resting. "It's like traveling from eastern Europe to western Europe along a highway," says Montgomery. "First you hear Polish, then you hear German."

Montgomery first heard the sounds of brain cells in the laboratory of Nobel laureate Sir John Eccles, neurophysiologist. "I just thought that was the coolest thing I'd ever heard, and I decided that's what I wanted to do."

Keep traveling on Montgomery's highway, and you'll make it to Grenoble, France, where the father of DBS (as Rezai calls him) teaches neurosurgery. In surgical procedures called pallidotomy and thalamotomy, surgeons destroy parts of the brain to stop tremors. During those procedures, the surgeons use an electrode to find the correct area to treat. In 1987, professor Alim-Louis Benabid, M.D., noticed that this stimulation of the thalamus mimicked the effect of the destructive surgery. So he developed DBS.

Last summer, Benabid agreed to serve as consultant staff member to the Cleveland Clinic Neurological Surgery Department, which he visits two weeks a year. Which is why he also is here in Operating Room Number Eleven, peering at Hammoud's computer.

Rezai and Hammoud eagerly demonstrate how the software morphs a CT scan with an MRI picture together with an overlay of topographical lines into a 3-D image of the brain, giving the surgeons a figurative road map to Russell's thalamus.

"The thalamus is the Grand Central Station of the brain," Rezai had told me earlier. It's this small area at the center of the brain, divided into 120 subregions, which routes the body's signals to move. Rezai expects that the electrode he implants in Russell's thalamus will "quench the chaotic neuron activity" that makes him twitch and quiver.

Imagine you discovered that your car had run out of gas. Thalamotomy, says Montgomery, is like pouring gas over the entire car, hoping that some will find its way into the carburetor. DBS, on the other hand, is like pouring a bit of fuel carefully straight into the carburetor to get it going again.

The electrode implanted in the brain is connected to a pacemaker-like stimulator the size of a flat pager, which is sewn into the patient's chest. This stimulator, worth $10,000, will modulate abnormal brain activity. In some patients, the stimulator is constantly on. In others, the patient can activate the stimulator with a magnetic card when he feels a tremor beginning. Soon, says Rezai, a patient using a modem and the Internet will be able to have his physician fine-tune the stimulator, wherever the physician may be.

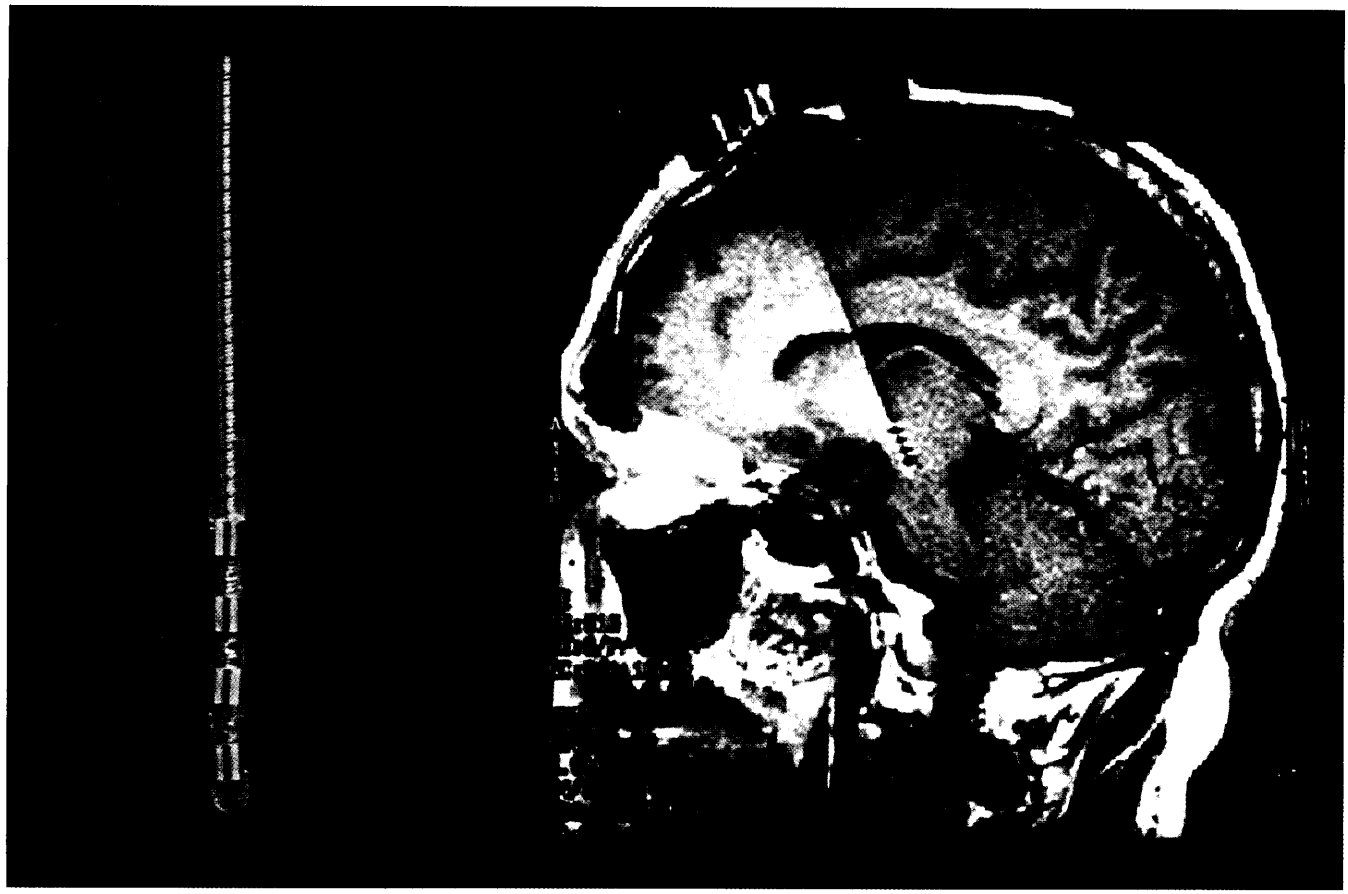
"The results are so sudden and obvious once you turn the stimulators on," says Marc Mayberg, M.D., chairman of the department of neurosurgery. "In my mind, this is a watershed time in the field of neuroscience. It represents the first time physicians have been able to improve or restore neurological function."

DBS not only restores the freedom of movement to patients, it is revolutionary because it is also reversible and does no damage.

And there's another benefit, says Montgomery. "What is clear in Parkinson's patients is that there is a long-term benefit that we can't explain just by stimulation. Patients are much better one month after implantation of the stimulator than they were prior to surgery. The results are incredible. But they're better at two months than they were at one month; they're better at three months than at two months." Something is affecting the degenerative process, he says, admitting that the neurosurgeons don't know what makes DBS work, although they do know it helps patients.

Less than a mile away, research scientist Warren Grill is trying to find out why. "We're taking a step back and addressing a fundamental question," says Grill, who holds a Ph.D. and is Elmer Lindseth assistant professor of biomedical engineering at Case Western Reserve University. He's also the director of the Cleveland Functional Stimulation Center, a consortium of local medical centers that's brought together the Clinic, Case Western Reserve, the Louis Stokes Cleveland VA Medical Center and MetroHealth Medical Center to share research and clinical experience regarding new brain therapies.

Grill received a $1.6 million, five-year grant from the National Institutes of Health to answer this fundamental question: Which neuronal elements are affected by the stimulation – the local neuron cells touched by the electrode or the passing axon output



Deep impact: The deep-brain stimulator (left) is an electrode the size of a hair; the MRI shows the trajectory of the stimulator implanted in the subthalamic nucleus.

flowing between those cells? He uses computer-based models to do his testing and relies on Dr. Montgomery's clinical research to corroborate the computer. Once Grill and Montgomery determine which neuronal elements are affected by the stimulation, they'll work on the technology of the stimulation.

"Not new technologies for placing the electrodes in the brain," says Grill, "but making the clinical procedure less reliant on the precise location of the electrode." He foresees developing new shapes for the electrode as well as discovering a new wave form for the electrical pulse that does the stimulating. These new technologies are expected to increase the effectiveness of the stimulation while reducing unwanted side effects.

Sixty-seven-year-old Rudy Mueller is among those patients who are walking because of the current techniques. Before his August 1999 DBS surgery, Parkinson's disease had reduced him to crawling around on his knees. He took up to fifty pills a day to treat his tremors. "My life would be at the end now," he says. With DBS, he's able to walk with a cane, and even drive himself around his Seven Hills neighborhood. "Now, with my stimulator, I have no shaking whatsoever." He takes only a handful of pills these days, and he's grateful that his insurer, Kaiser Permanente, referred him to the Clinic and paid for the expensive surgery.

"The hope is that all doctors will one day be as comfortable prescribing electricity as they are prescribing medication," says Montgomery.

Rezai expects that, any day now, the FDA will grant final approval to DBS as a standard treatment for Parkinson's tremor. Other emerging areas for DBS use are epilepsy, chronic pain and obsessive-compulsive disorder.

In June 2001, Cleveland will host the international symposium *Functional and Restorative Neurosurgery: Defining the Future*. "Fifty of the world's leading authorities and pioneers on neuromodulation – the All-Stars – will be here for three days," says Rezai. "It will be exciting to bring these minds together to chart the course of neurosurgery."

One possible innovation, says Mayberg, is a "radical on-line collaboration to share data intra-operatively, in real time. Dr. Benabid has a grant from Telecom France. He'd be on-line with a video link and would be looking at the same information on his computer. It may [seem] farfetched, but someday he might even drive the movement of the electrode. As the technology expands, we may become a center for doing operations around the country."

And then, probing minds will listen in as the brain talks.

Former Northern Ohio Live *editor Anton Zuiker recently returned from two years on a remote island in the Pacific with the Peace Corps.*