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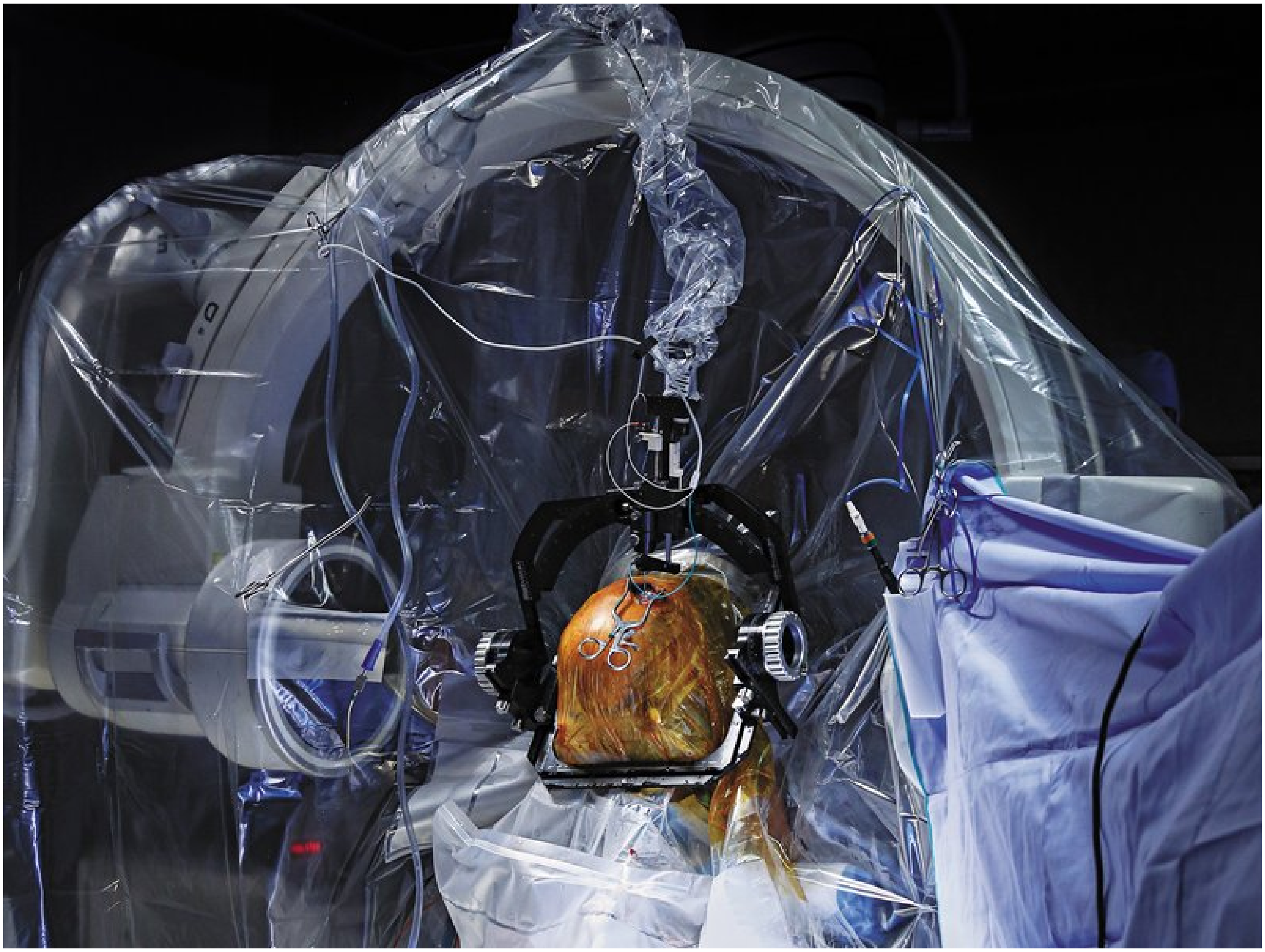

A neurosurgeon's view during a brain operation: The head is held in place and covered with an adhesive drape containing iodine, which prevents infections and explains the orange tint. (Bob Croslin)

Inside the Science of an Amazing New Surgery Called Deep Brain Stimulation

The most futuristic medical treatment ever imagined is now a reality

By David Noonan
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Like most people in need of major surgery, Rodney Haning, a retired telecommunications project manager and avid golfer, has a few questions for his doctors. He wonders, for example, exactly how the planned treatment is going to alleviate his condition, a severe tremor in his left hand that has, among other things, completely messed up his golf game, forcing him to switch from his favorite regular-length putter to a longer model that he steadies against his belly.

"Can anyone tell me why this procedure does what it does?" Haning asks one winter afternoon at UF Health Shands Hospital, at the University of Florida in Gainesville.

"Well," says Kelly Foote, his neurosurgeon, "we know a lot, but not everything."

The vague answer doesn't seem to bother Haning, 67, an affable man who has opted for the elective brain surgery. And it's hard to fault Foote for not going into greater detail about the underlying science, since he is, at that very moment, boring a hole in Haning's skull.

"Can you hear the drill?" Foote asks his patient as he presses the stainless steel instrument against bone. When Haning, whose head is immobilized by an elaborate arrangement of medical hardware, asks why it doesn't hurt to have a dime-size hole drilled in his skull, Foote calmly explains that the skull has no sensory nerve receptors. (The doctors numb his scalp before making the incision.)

The two continue to chat as Foote opens the dura—"It's the water balloon that your brain lives in," he says. "It's sort of like a tough leather, for protection"—and exposes Haning's brain.

Deep brain stimulation, or DBS, combines neurology, neurosurgery and electrical engineering, and casual conversations in the operating room between doctors and their wide-awake patients are just one of the surprises. The entire scene is an eerie blend of the fantastic and the everyday, like something from the work of Philip K. Dick, who gave us the stories that became *Blade Runner* and *Total Recall*. During surgery, DBS patients are made literally bionic. Tiny electrodes are implanted in their brains (powered by battery packs sewn into their chests) to deliver a weak but constant electric current that reduces or eliminates their symptoms. DBS can improve a shaky putting stroke; it can also help the disabled walk and the psychologically tormented find peace.

More than 100,000 people around the world have undergone DBS since it was first approved, in the 1990s, for the treatment of movement disorders. Today, besides providing relief for people with Parkinson's disease, dystonia (characterized by involuntary muscle contractions) and essential tremor (Haning's problem), DBS has been shown to be effective against Tourette's syndrome, with its characteristic tics, and obsessive-compulsive disorder. Add to that a wave of ongoing research into DBS's promise as a treatment for post-traumatic stress disorder and other neuropsychiatric conditions, as well as early signs that it may improve memory in Alzheimer's patients.

Suddenly it's one of the most exciting treatments in modern medicine. With seemingly millions of potential DBS patients, it's easy to imagine a future where brain implants may become as common as hip replacements.

As co-directors of the UF Center for Movement Disorders and Neurorestoration, Foote and neurologist Michael Okun are at the forefront of the DBS field, refining operating techniques and establishing a rigorous standard of care that attracts patients from around the country and the world. Since teaming up at UF in 2002, Okun and Foote have done nearly 1,000 DBS procedures together and grown their two-man effort into an interdisciplinary program with more than 40 staffers, including eight neurologists, a psychiatrist, a neuropsychologist and physical, speech and occupational therapists. The treatment, for patients whose symptoms aren't sufficiently controlled by medication, carries the usual risks associated with neurosurgery, including stroke and infection. Side effects range from headaches to speech and memory problems, and, in some cases, seizures. But Okun says more than 90 percent of their patients rate themselves as "much improved" or "very much improved" on standard postoperative outcome scales.

In the 12 years since they joined forces, Okun and Foote have seen DBS evolve, in Okun's words, "from crazy, to kind of cool but not completely accepted, to accepted." Okun, 42, recalls: "When I first got hired here, my chief said to me, 'You're a nice kid, you're a polite kid, but don't embarrass us.'"

Together, Okun and Foote breached the wall that has forever separated neurology and neurosurgery—blew it to smithereens, actually—and formed a partnership that defies tradition as it advances the science of DBS. While it might sound logical to the layman—of course neurology and neurosurgery go together—it's hard to overstate how very differently the two disciplines have been practiced. And perceived. Foote, 48, whose smile comes easily and often, captures the old thinking with an old joke: "What's the difference between neurology and neurosurgery? Well, both types of doctor treat people with disorders of the central nervous system. And if there's something you can do about it, it's neurosurgery. If there's nothing you can do about it, it's neurology.'"

It's all too true that neurologists have had to deal with more than their share of incurable conditions with unknown causes. Multiple sclerosis, Lou Gehrig's disease, myasthenia gravis. The list goes on, and watching Okun at work in the OR during a DBS procedure, it's as if he's out to make up for all those decades of frustration in the specialty he loves. "Mike has a very surgical personality," says Foote. "And I am much more of a neurologist than most neurosurgeons."

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Okun and Foote met as residents at UF in the 1990s. Foote grew up in Salt Lake City and was in high school there when, in 1982, the town produced the biggest medical story in the world at the time—the saga of Barney Clark, the first human recipient of a permanent artificial heart, the Jarvik 7. The operation was performed at the University of Utah, and though Clark died after 112 days, Foote's fascination with the case endured. He earned a degree in materials science and engineering at the University of

Utah, intending to become an inventor of artificial organs. He entered medical school at Utah, where two things changed his course. First, he realized that biological solutions such as improved antirejection therapies, not mechanical organs, were the future of transplant medicine. Second, he did his neurosurgery rotation and saw the brain for the first time. “What could be more fascinating than the brain?” he asks.

Okun’s path was also turned in medical school. Though he majored in history as an undergraduate at Florida State University, he made a late decision to go to med school and become a “black bag doctor,” a general practitioner caring for families and making house calls. “Then I got my first introduction to the brain,” he recalls, “and I said, ‘This is really cool.’”

Twenty years later, his enthusiasm is fresh as he describes his neurological satori. “A lot of people were saying all these pathways and everything are really complicated, and they just wanted to get through the class and get a grade. But to me it made perfect sense. You could localize diseases and networks within the brain and figure out where things were and actually make a difference.” Later, as Okun’s interest in movement disorders grew, he realized he had been exposed to them his whole life. “The Jews have some of the highest incidences of movement disorders,” says Okun, who grew up in a Jewish family in West Palm Beach, Florida. “If you go to temple you see it, a lot of people are blinking, they have tics, they have tremors. One of the reasons I was fascinated by this field is I would look back and remember seeing people shaking and shuffling and thinking to myself, ‘Why is that?’”

He knows the answer to that question now. “There’s an abnormal conversation going on between different regions of the brain,” he explains. DBS interrupts those abnormal conversations. The challenge for Okun and Foote is to identify the tiny spot in each patient’s brain where the electrodes will do the most good, to locate, amid the cacophony of a hundred billion chattering neurons, the specific neural network that is causing the patient’s problem. “Location is everything,” says Okun. “A couple of millimeters in the brain is like the difference between Florida and California.”

Before setting up shop at UF, Okun and Foote both studied with DBS legends. Okun trained at Emory University with neurologist Mahlon DeLong, who pioneered the “brain circuit” approach to understanding and treating movement disorders. (DeLong is one of six 2014 recipients of a $3 million Breakthrough Prize in Life Sciences, created last year by Mark Zuckerberg and other Silicon Valley leaders to recognize major achievements in medical science.) Foote, after completing his residency, went to Grenoble, France, where he worked with Alim-Louis Benabid, who developed DBS as a treatment for Parkinson’s and performed some of the first procedures in the early 1990s. Foote then joined Okun at Emory, where the two continued their DBS training with DeLong and neurologist Jerrold Vitek.

Now, as the two of them try to better understand and manipulate neural circuitry, they are working in what could be called a golden era in brain science. Each week seems to bring news of another advance, like a report in January from England affirming the effectiveness of transcranial magnetic stimulation as a treatment for acute migraine, which followed reports about the successful use of the non-invasive procedure for depression and some symptoms of schizophrenia. And research interest is booming too, as evidenced by the ambitious, multidisciplinary White House BRAIN Initiative. DeLong, after four decades studying the functional organization of the brain and neuromodulation, has never seen anything like it. “The pace of change and discovery is just unprecedented,” he says. “We’re forging really great advances in almost every disorder you look at, for both neurology and psychiatry. And this will pay off.”

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Surgeons, as a rule, do not like sharing power. The stereotype of the domineering OR general is rooted in the simple fact that cutting open human bodies is a high-risk business and someone needs to be in charge. Foote, tall and commanding in his scrubs, gladly cuts against this expectation in his collaboration with Okun. He treats the neurologist as an equal partner in the procedure, a co-operator, to be exact, though the neurologist does not scrub in or get near the sterile field that surrounds the opening in the patient’s skull.

Okun, several inches shorter than Foote, is focused and intense in the OR, a forceful presence from the moment he enters, though he doesn’t say much at first. On this day, he is too busy studying the computer screen where Rodney Haning’s MRI is being compared with a brain atlas that Okun, Foote and other UF colleagues created with data from the dissection of dozens of postmortem brains; because every brain is slightly different, matching structures in Haning’s brain with the atlas helps the doctors map their targets. Standing side by side, Okun and Foote discuss their planned approach, pointing to familiar landmarks, which are outlined on the screen in bright red, green, yellow and blue.

When the skull has been opened, Foote slowly feeds a microelectrode on a hair-thin wire down into Haning’s brain. This is not the lead that will be permanently implanted in the brain; rather, it’s a kind of electronic advance scout, a radio receiver that picks up and amplifies the electrical signals of individual brain cells, while canceling out ambient electrical noise. As the probe moves deeper into the brain, the sound of the cells fills the OR, like static from deep space. Okun, who has taken up his position at the patient’s side, manipulates Haning’s left arm and fingers, and strokes his arm, chin and lips, triggering electrical activity in the brain. As he does this, he listens to the screech of individual neurons—their electrical signatures—as they are pierced by the microelectrode. With his trained ear, Okun distinguishes between normal neurons and the abnormal neurons that are causing

Haning's tremor, and he guides Foote to their target, a malfunctioning network of cells located in Haning's thalamus, near the center of his brain, about four inches down from the hole in the top of his head. "That's a tremor cell," he says at one point. "Can you hear it?"

Keeping movement disorder patients awake during DBS procedures makes it possible to track the effects of the surgery in real time. One of the quirks of the treatment is that the operation itself alters brain tissue and interrupts the abnormal signals, reducing the patient's symptoms before the current is even turned on. (This temporary effect is an echo of past practice; years ago, before DBS, surgeons treated movement disorders by creating tiny lesions in the brain.) Several times over the course of his operation, Haning uses his left hand to draw spirals on a clear plastic clipboard that is held up for him. His first spiral, made before the procedure begins, is jagged, unsteady. His last one is smooth, the work of a tremor-free hand.

As the operation winds down, with the lead in place in Haning's brain, a pleased Okun tosses Foote a compliment. "Kelly, I don't know how you did it, but you're all hand," he says, referring to the way Foote hit the target area, the circuit that was causing the tremor in Haning's left hand.

"Imagine that," Foote replies, deadpan.

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DBS isn't an option for everyone. It offers hope to selected patients who, despite expert medical management, remain disabled by their symptoms. While it usually works, it is hardly a panacea. It's brain surgery, after all, arguably the most invasive of all invasive procedures. And besides the usual surgery risks, it requires follow-up outpatient surgery every four years to replace the battery pack.

But it has showed itself as an effective and generally safe treatment for many, including Rodney Haning. With those successes, Okun and Foote, like other leaders in the field, are looking beyond movement disorders. That's why they added the word "neurorestoration" to the name of their UF treatment center, and why they are already performing experimental DBS procedures on patients with obsessive-compulsive disorder, Tourette's syndrome and Alzheimer's disease.

Similar DBS research is going on at academic medical centers across the country. DBS has even attracted attention from DARPA, the research arm of the Department of Defense, which is launching a five-year effort specifically targeting four neuropsychiatric conditions—PTSD, major depression, borderline personality disorder and general anxiety disorder—as well as traumatic brain injury, addiction and chronic pain.

It's a dreadful and daunting list. It evokes a universe of suffering even as it speaks to the promise inherent in every successful DBS procedure: If we can do *this*, then perhaps we can do *that*. Faced with the challenge to take DBS further, Okun and Foote offer a measured view of the state of their art. "Right now, our understanding of the circuitry in the brain is fairly rudimentary," says Foote. The technology is "pretty crude," especially when compared with the human brain, with its 100 billion neurons and an estimated 100 trillion synapses.

In the past, Okun explains, the big debate in the field was whether DBS worked by inhibiting abnormal circuits or exciting other brain activity. Both sides ended up being right: The neurons closest to the implanted leads are inhibited by the electrical current, while axons leading away from the targeted cells are stimulated. In addition to these changes, says Okun, in the last few years we've learned that DBS also alters brain chemistry and blood flow, and even leads to the growth of new brain cells. And recent studies using electroencephalography show that DBS causes what Okun calls "neurological oscillations," disease-specific changes in the electrical wave patterns that ripple through the brain. In Parkinson's disease, for example, DBS suppresses the beta wave, while in Tourette's syndrome, it stimulates the gamma wave.

Okun and Foote have seen firsthand the power of their "pretty crude" technology to affect mood and emotion. They even filmed it and presented it to an audience as part of a talk they gave in 2012. In the video, a woman undergoing a DBS operation to alleviate her debilitating obsessive-compulsive disorder beams with joy and laughs when, during the normal course of the successful procedure, Okun and Foote "tickle" a region near her nucleus accumbens, a part of the brain associated with pleasure, reward, motivation and other complex phenomena.

"Describe what you're feeling right now," Okun says. With an ecstatic smile on her face, in a voice giddy with joy, the woman replies, "I feel happy."

It's an extraordinary moment, and a powerful demonstration of DBS's potential as a treatment for disorders like major depression. It's also unsettling, a peek into a possible future where human happiness is the product not of the experiences and relationships that make up a life, not even of mood-altering medications, but of an elective surgical procedure, a face-lift for the brain.

Okun and Foote are acutely aware of the ethical issues raised by their DBS work. They have adopted a guiding principle that defines their goals and proscribes anything that might be considered outside the bounds of proper medical practice: The purpose of DBS, they insist, is to alleviate pain and suffering. It's a clear standard. The question is, will it endure over time as the specialty continues to evolve?

Standing just outside the OR after Rodney Haning's operation, still in his scrubs, his surgical mask dangling from his neck, Foote tries to imagine a day when healthy, normal people will choose to undergo DBS in order to enhance their lives. He understands the appeal. Referring to early results from Alzheimer's research, he says, "What if we were able to make people remember better? Who's not going to want that?"

But it's still brain surgery, he argues. "Can you imagine," he says, "if I take a perfectly normally functioning human being who wants to have some enhancement, and I do an operation, and I hurt them, and they end up a not perfectly normally functioning human being? Imagine the liability there." He can't see how the surgical boards and the FDA would ever allow such a thing. Of course, "If it ever got to the point where it was essentially risk-free," he says, "then you would let the line go a little further, probably."

Foote ponders that idea as the subject of cosmetic surgery comes up. Sixty years ago, plastic surgery, a technically challenging specialty with one of the longest training regimens in medicine, was centered on the treatment of facial trauma and disfigurement. Today, ordinary people think nothing about undergoing multiple cosmetic procedures to make themselves more attractive, and surgeons are happy to perform them.

"That's actually a really good analogy," Foote says. "I hadn't thought of it that way. If you're not dysfunctional, should you be able to get functional surgery? And I think DBS is going to be a similar battleground." He hesitates a moment, then finishes the thought. "And we will ultimately cave in. Just like we did with cosmetic surgery." This is a revelation for him, and not a good one. "I hadn't really gone that far in my head, but now that I think about the whole cosmetic surgery thing... yeah... goddamn."

Foote returns from the future and his mood brightens immediately when he's asked how it feels to watch patients like Haning leave the OR smiling and waving their tremor-free hands. "It's still a rush," he says, "every single time."

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A few days after his operation, Rodney Haning is back home in the Villages, the Florida golf community where he lives with his wife, Barbara Jo. He's been practicing in his den with his favorite putter, looking forward to a busy spring and summer playing the game he loves. He's tired from the surgery, but feels stronger every day. His tremor is gone, and he hasn't experienced any side effects from the ongoing treatment. Except for the small scars on the top of his head (his golf hat will cover them when he's back on the course), there are no signs of his recent adventure in the OR. "I've got absolute trust in those guys," he says of Okun and Foote. "I thought it was real neat during the operation when he said 'That's your tremor right there.' It's surreal, that's why I was chuckling every now and then." He pauses, recalling the details. Then, with a laugh: "There was a hole in my head."

About David Noonan

David Noonan is the author most recently of the Amazon Kindle Single .

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