SOUND SURGERY
Surgeons can now operate deep within the brain using focused beams of ultrasound, ushering in a new era of faster, safer, incision-free treatments

By Stephen J. Monteith, Ryder Gwinn and David W. Newell

Illustration by TATIANA PLAKHOVA
Carol Aldrich first noticed a slight tremor in her right hand when she was in her early 50s. Working for an optometrist in Port Townsend, Wash., a picturesque town on the Olympic Peninsula, Aldrich routinely performed delicate work with her fingers—replacing broken eyeglass lenses and repairing frames. At least initially, her tremor would come and go, leaving her sometimes unable to manage tiny screws and fragile settings. “I just thought I had had too much coffee,” the mother of three recalls.

Gradually, though, her shaking grew more persistent. “After a while, it was with me all the time,” Aldrich says. She visited her doctor who diagnosed essential tremor, which today is the most common movement disorder, found in about 5 percent of people older than 64 years worldwide. The cause of the condition is unknown, but it often runs in families. Its hallmark tremors are typically small, rapid, back-and-forth movements—often oscillating more than five times a second. They most frequently affect the hands and head but can also strike other parts of the body and the voice; they usually worsen with time.

For Aldrich, the trembling progressed to her left hand after about five years. Within a decade it had advanced to her head. Her symptoms eventually shook her self-esteem, too. “The tremor made me feel old,” she says. Although the disorder is sometimes called benign essential tremor, for many patients it is anything but benign: the vast majority, about 85 percent, say the tremor causes a significant change in their life. About one in four, according to a 1994 study by neurologists at what is now the University College London Institute of Neurology, have to change jobs or take early retirement. More than half of the people afflicted cannot find work, and one in three report withdrawing from social life.

Unfortunately, drug treatment fails to satisfactorily control essential tremor in up to 50 percent of all patients. Like many sufferers, Aldrich sought relief from several medications, including propranolol—more commonly used to treat high blood pressure and anxiety—and primidone, a first-line therapy for essential tremor that is also prescribed as an antiseizure medicine. The former helped for only a little while, and the latter involved side effects that Aldrich found intolerable, such as lethargy.

Then, in 2013, Aldrich saw a news program on television about an experimental new tremor treatment called focused ultrasound, or FUS, that used sound waves to destroy the malfunctioning nerve cells responsible for her condition. The report said that results from early clinical trials at the University of Virginia were promising. So Aldrich went online and signed up to participate in a future study.

In recent years growing numbers of researchers around the world have begun experimenting with focused ultrasound. The accumulating evidence suggests that the technology could soon make painless, bloodless brain surgery a reality and revolutionize how many conditions are treated. Patients with cancers and movement disorders might avoid invasive procedures, radiation and lengthy hospital stays and instead be treated with relatively low risk, incision-free sonic surgeries. Focused ultrasound has been approved in Europe for treating essential tremor, a disorder called benign essential tremor, which today is the most common movement disorder, found in about 5 percent of people older than 64 years worldwide. The cause of the condition is unknown, but it often runs in families. Its hallmark tremors are typically small, rapid, back-and-forth movements—often oscillating more than five times a second. They most frequently affect the hands and head but can also strike other parts of the body and the voice; they usually worsen with time.

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sential tremor, tremor caused by Parkinson’s disease, and neuropathic pain. In the U.S., the use of FUS in brain surgery is still confined to clinical trials. Our institution is one of several participating in the first pivotal trial of focused ultrasound for essential tremor; we expect to release results in 2016. For people such as Aldrich, who are not helped by medication and have had no good surgical options available to them, the promise is enormous.

Making Waves

Vibrations in the air create nearly all the sounds that we hear. When a guitarist plucks a string, for example, its rapid back-and-forth movement is transmitted to the surrounding air molecules, which then relay the vibrations to more neighboring molecules, and so on. This creates a mechanical wave of compression and decompression that ripples through the air. When those sound waves reach our ears, their mechanical energy vibrates the thin membrane of our eardrums at the same frequency as the guitar string, which our brain interprets as a musical note. With standard tuning, the low E string of a guitar vibrates back and forth about 82 times a second, or, in scientific notation, at 82 hertz. The lowest sound most of us can hear is about 20 Hz; the highest is about 20,000. Any sound above what we can hear is, by definition, ultrasound.

Since the early 20th century, people have used ultrasonic waves to “see.” At high energy levels, however, sound waves can generate enough heat to temporarily disable cells. At even higher temperatures, the tissue is essentially cooked. To generate enough energy and heat demands more than a single ultrasound beam. So-called focused ultrasound works by concentrating the power of hundreds of ultrasound beams on a single spot. The result is a unique surgical tool. In pioneering work conducted during the 1950s and 1960s, William Fry, a physicist at what is now the University of Illinois at Urbana-Champaign, working with neurosurgeon Russell Meyers, then at the State University of Iowa, treated Parkinson’s patients using focused ultrasound to disable the substantia nigra and ansa lenticularis, two structures deep in the brain that malfunction in that disease. Until quite recently, though, such sonic brain surgeries had major drawbacks.

The skull presented the biggest challenge because sound does not traverse bone well. In fact, energy from ultrasound passing through the skull can be absorbed and converted to heat and can cause burns. In addition, the curving, irregular shape of the skull tends to bend, or diffract, the individual ultrasound beams, just as rippled glass will distort an image. This diffraction makes it difficult to fo-
HOW IT WORKS

At the Swedish Medical Center, based in Seattle, we use a device called the ExAblate Neuro, developed by INSIGHTEC, an Israeli company that is also supporting our research with this technology. The device integrates a phased array of focused ultrasound beams and an MRI scanner so that they work as a unit.

Before treatment, a patient undergoes a CT scan to detail the shape, thickness and density of his or her skull, factors that determine how well the sound waves will traverse the bone. This information is then fed into a computer, which uses the data to adjust the output of the phased array so that it corrects for the skull’s diffraction of individual beams, and they all emerge from the bone focused on the same target.

At the beginning of the procedure, we place a special metal frame on the patient’s head to prevent any movement. Then the patient lies down and slips into a helmet containing transducers that convey the ultrasonic beams (1). This helmet also features a dome-shaped silicon diaphragm, which rests on the scalp. Cold water circulating through the diaphragm has two functions: it makes it possible for the sound waves to travel from the transducers into the head, and it prevents the scalp from being burned by the heat created as the ultrasound passes through the skull.

Once the patient is inside the MRI scanner (2), a radiologist or surgeon focuses the transducers on the target (3). To begin, low-energy sound beams warm the brain area in the crosshairs—a temperature change that shows up on the MRI scan. If the wrong spot “lights up” under these test beams, the device’s focus can be adjusted in submillimeter increments. Once the correct positioning is confirmed, the higher-intensity therapeutic ultrasound beams start to fire (4) until the targeted tissue reaches about 60 degrees Celsius (140 degrees Fahrenheit)—at which point it coagulates (5). The neuroradiologist then retargets the array to the next area to be treated, and the process repeats. To destroy a pea-sized ventral intermediate nucleus (VIM) of the thalamus to treat essential tremor requires six to 20 cycles of high-intensity firing, which can take about five hours to complete.

Because the brain feels no pain, a patient can be awake throughout this procedure. This makes it possible to see if the treatment is having the desired effect. For example, a patient with essential tremor will see his or her tremor lessen as the procedure progresses. It also makes it possible to see if the treatment may be causing any unwanted side effects. If, for instance, during treatment, the sound waves inadvertently start to heat nearby sensory centers, the patient may report numbing in the face. Neurosurgeons can then switch off the ultrasonic beams, recalibrate and retarget before causing any permanent harm.

—S.J.M., R.G. and D.W.N
cus the sound beams and reduces the energy they can impart. As a result, early ultrasound treatments of brain disorders required that surgeons first remove part of the skull—a procedure called a craniotomy—to make a window through which the sound waves could pass. These early procedures took up to 14 hours, with no guarantee that the sound waves were reaching the right location. Thus, although researchers made considerable progress using ultrasound to treat targets that were not encased in bone—benign breast tumors, uterine fibroids and enlarged prostates—similar treatments for brain conditions lagged behind.

Then, in the 1990s, scientists made two major advances. First, several research groups, including a team at General Electric then under the leadership of engineer S. Morry Blumenfeld, began to couple focused ultrasound with MRI so that they could be used in concert to direct the beams more effectively. Second, biomedical physicist Kullervo Hynynen and the late neuroradiologist Ferenc A. Jolesz, both then at Brigham and Women’s Hospital in Boston, developed phased-array systems, which in essence made it possible to coordinate the timing, or phase, of the sound waves to correct the diffraction caused by the skull’s irregular shape, thus removing the need for a craniotomy.

The result was a device of extraordinary power, allowing its operators to focus ultrasound beams with great precision and then watch how the beams altered the target tissue in real time. Because the coordinated MRI images can reveal temperature changes in real time, it is possible to use harmless, low-intensity ultrasound emissions to warm the tissue first and see exactly where the ultrasound beam is focused. Surgeons can then adjust the array—making corrections smaller than a millimeter, if necessary—before firing, dramatically reducing the risk of any accidental damage [see box on opposite page]. They can also use low-intensity ultrasound to briefly stun areas of the brain and test that they are not inadvertently targeting regions involved in important functions, such as speech. And because the brain feels no pain, the focused ultrasound procedure is completely painless, aside from some mild discomfort from the frame that holds the head in place.

Treating Tremor

Traditionally surgeons have most easily plied their craft on areas close to the brain’s outer layer, or cortex. Structures deep within the brain—including those implicated in essential tremor, Parkinson’s and some neuropathic pain disorders—have posed a much greater challenge. Focused ultrasound, however, actually works best on these hard-to-reach spots. Closer to the cortex, the ultrasound beams must travel at a shallower angle, causing them to have to travel through more of the skull and making them more likely to miss their mark.

To remedy essential tremor, most treatments seek to destroy or disable one of the brain’s two ventral intermediate nuclei (VIM). These pea-sized clusters of neurons, located within the thalamus, near the very center of the brain, manage information about the position of our limbs in space, playing a vital role in the coordination and planning of movement. In essential tremor, the transmission of this information becomes garbled. And as the brain constantly tries to adjust and overcorrect that garbled information, it creates an oscillatory effect—which manifests as the condition’s characteristic trembling. Removing the VIM, a procedure called a thalamotomy, can significantly reduce the tremors, but it can also cause serious side effects—including speech and balance problems, confusion and paralysis.

To minimize the risk, surgeons attempt to silence the faulty communication in only one of the VIM—usually the circuit that controls movement in the dominant hand or the side that is most seriously affected. Currently there are several ways to proceed. They can slip a catheter into the brain and, when the tip reaches a VIM, heat it to destroy the tissue. They can damage a VIM with high-energy radiation beams. Or they can use deep-brain stimulation, placing an electrode in the target VIM to deliver a low-voltage current that disrupts the nerve signals there. All three approaches can alleviate tremors, but drilling into the skull to place catheters and electrodes poses a

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risk of bleeding and infection. High doses of radiation can kill or damage healthy tissues.

In contrast, focused ultrasound requires no surgery or radiation and can pinpoint brain areas smaller than a grain of rice. In a pilot study published in 2013, neurosurgeon W. Jeffrey Elias of the University of Virginia and his colleagues, including one of us (Monteith), put focused ultrasound for thalamotomy to the test. In the study, which involved 15 patients with essential tremor, they found that it could destroy a VIM and decrease tremor and disability just as well as any existing method but with none of the associated risks.

A New Surgical Era

Beyond tremor treatments, neurosurgeons around the world are testing focused ultrasound in a range of incision-free brain operations. Promising applications abound. This technology could be used to destroy or alter brain areas associated with epilepsy, Parkinson’s and pain conditions, shutting down problematic neural circuitry without harming neighboring cells. It might even be applied to neuropsychiatric diseases. In South Korea, clinical trials are under way to test the use of focused ultrasound to quiet a part of the prefrontal cortex thought to be overactive in depression and to shut down other deep-brain regions involved in obsessive-compulsive disorder.

Focused ultrasound shows particular potential for cancer treatment. In 2014 Monteith, working with his colleagues at the Swedish Neuroscience Institute in Seattle, performed the first surgery using focused ultrasound to treat a metastatic brain tumor—that is, a tumor that appears in the brain after cancer cells have spread from elsewhere in the body. And in the same year, a team led by neurosurgeon Javier Fandino of Cantonal Hospital Aarau in Switzerland and neuroradiologist Ernst Martin of University Children’s Hospital Zurich demonstrated that they could use focused ultrasound to partially destroy a glioblastoma, a common and particularly deadly brain cancer.

The technology might also give pharmaceutical treatments a boost [see box above]. Many drugs cannot enter the brain because of the blood-brain barrier—in essence, a wall of cells that line the blood vessels within the brain. These cells,
called endothelial cells, form tight junctions with one another and filter out what cannot pass in between them. In general, they block large molecules that dissolve easily in water—including many important anticancer drugs, therapeutic proteins and antibodies. But research shows that focused ultrasound can temporarily pry the endothelial cells apart without destroying them, creating openings wide enough for bigger molecules to enter the brain. Researchers in Canada are now evaluating using this approach to treat Alzheimer’s disease in preclinical studies. By briefly suspending the blood-brain barrier, focused ultrasound may give antibodies greater opportunity to attack the plaques involved in the disease.

Other scientists are hopeful that this trick may similarly increase the efficacy of some chemotherapies. Significantly, focused ultrasound disrupts the blood-brain barrier only in a specific location—namely wherever a surgeon directs the sonic beams. Thus, it is possible to apply a drug to a particular spot—say, a malignant growth—and spare the rest of the brain from any toxic side effects. Animal studies by neuroscientist Nathan J. McDannold of Brigham and Women’s and others have demonstrated that focused ultrasound can disrupt the blood-brain barrier to allow therapeutic doses of a chemotherapy drug, doxorubicin, to enter the brain, suggesting such an approach could be effective in treating glioblastomas and other brain cancers in humans.

Relief at Last

When Aldrich first came to the Swedish Neuroscience Institute, she was enrolled in a randomized clinical trial. So she knew that she might be assigned to the control group, meaning she would undergo a fake procedure in which the team would do everything involved in a real treatment except administer the ultrasound. As it turned out, she was indeed in the control group. “I knew it was a sham,” Aldrich says. “During the procedure, they would ask me to draw a spiral with pen and paper within a guided diagram. That’s really hard if you have a tremor, and my spirals were not getting any better.” After the trial study concluded, though, the hospital invited volunteers from the control group to undergo the real treatment, and so Aldrich returned. In her case, the surgeons targeted the VIM involved in controlling movement in her dominant (right) hand. “I could hear the MRI machine and hear the water circulating through the cap device I wore, and I had expected I would feel some heat, but I didn’t feel anything going on inside my head,” she remembers. “But with each shot, my spirals got better. And they got better and better, and I thought, ‘Hallelujah! I’m cured!’” Today Aldrich continues to have tremors in her head and left hand but none in her right hand. “I can write,” she says. “I can pour coffee. I can do everything with that hand again.” Not every patient responds as well as Aldrich did, but successful treatments often at least significantly reduce tremors. Sometimes the tremors recur, but they are usually less severe and less disabling when they do.

Despite such encouraging results, for the moment focused ultrasound for treating brain disorders remains experimental. But this technology could radically change how we treat a wide range of ailments relatively soon. It is part of an emerging arsenal of surgical tools, including beam therapies that can demolish tumors with subatomic particles. If their promise is borne out, neurosurgeons will increasingly set aside their scalpels and drills and routinely perform painless, bloodless, incision-free operations. The term “revolutionary” is often overused to describe new innovations, but it is hard to find another term that better describes how focused ultrasound is likely to change the field of brain surgery. Just ask people like Carol Aldrich.

FURTHER READING

- Focused Ultrasound Foundation: www.fusfoundation.org
- From Our Archives
- Breaking the Brain Barrier. Jeneen Interlandi; Scientific American, June 2013.