Conversing with the BRAIN

Responsive Neurostimulation Helps Prevent Partial Epileptic Seizures

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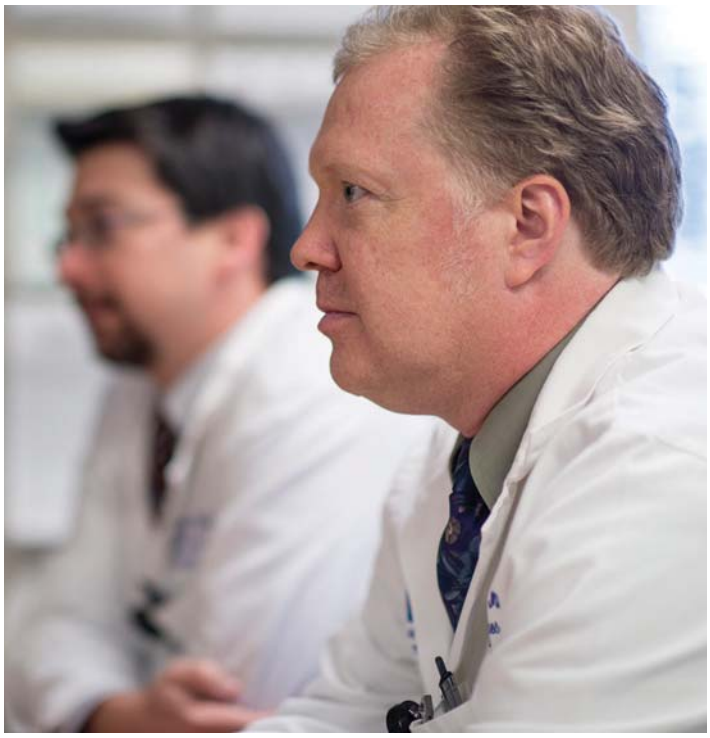
The neurons of the brain communicate with one another through electrical signals. In recent years, therapies for a variety of conditions, ranging from Parkinson's disease to depression, have been developed that intervene in that communication by sending an electrical charge, either via an implanted microprocessor (deep brain stimulation, vagus nerve stimulation) or through an external magnetic coil (transcranial magnetic stimulation). Transmitting an electrical charge to the specific areas of the brain thought to be dysfunctional has helped stop tremor in Parkinson's disease, prevent epileptic seizures, and provide relief for treatment-refractory depression.

As impressive as these advances have been, the communication with the brain that they have achieved has been one-way, and the "message" or electrical stimulation that the implanted devices have been able to provide less than nuanced. For example, the implanted microprocessor in deep brain stimulation continues to send the same strength of charge at the same frequency until its parameters are reset during a clinic visit. The physician must "close the loop," adjusting the settings based on a clinical assessment.

In contrast, the responsive neurostimulator, approved in November 2013 by the US Food and Drug Administration (FDA) for treatment of medication-refractory partial seizure epilepsy with no more than two identified epileptogenic foci, is able to engage in a two-way conversation with the brain, detecting the electrical signature of an impending partial seizure and then delivering an appropriate charge to disrupt that signature and prevent the seizure. The device itself is able to close the loop based on its monitoring of brain activity.

Dr. Edwards discusses the potential of responsive neurostimulation in the online edition



"We are actually having a conversation with the human brain instead of engaging in a one-directional communication." —Jonathan C. Edwards, M.D.

Just as the telephone marked a quantum leap forward over the telegraph in enhancing our ability to communicate with one another, responsive neurostimulation marks an important step forward in our ability to communicate with and influence the brain. "We are actually having a conversation with the human brain instead of just engaging in a one-directional communication," notes **Jonathan C. Edwards, M.D.**, Professor in the Department of Neurosciences and Director of MUSC's Comprehensive Epilepsy Center.

A small microprocessor in a thin, flat, metal shell is implanted in the skull and attached via one or two wire leads to strip or depth electrodes. The strip electrodes are placed on the surface of the brain, whereas the depth electrodes can be placed deep inside the brain tissue. Both are placed stereotactically at the source of the patient's seizures. In contrast to electroencephalography, which records the brain's signals at the scalp, electrocorticography, made possible by these surface and depth electrodes, directly records the brain's activity without interference by the skin and skull.

"In electroencephalography, it's a propagated sort of distant pattern that you are recording. Well, of course, seizures aren't generated on your scalp. It's like recording volcanic activity from out in the atmosphere, but the seizure is being created in the volcano, and these depth electrodes allow us to get down into the volcano," explains Dr. Edwards.

How Does It Work?

The implanted device continuously records the cortical activity of the brain and that information is stored on the microprocessor. When a patient experiences a seizure, he or she is asked to hold a special magnet near the implanted device, which marks the seizure's occurrence. The patient can "download" this recorded information by waving a special wand over the base of the skull where the device is implanted. These data can then be sent to a secure website, where they can be accessed by his or her physician.

The electrical signal of partial seizures can vary greatly among patients. For instance, some patients have seizures that begin with a very low amplitude and a very fast frequency in one spot and gradually evolve into a higher-amplitude, slower-frequency signal in the surrounding area, whereas in others the seizure begins with a set of spikes or with sinusoidal rhythmic frequency. By analyzing the recorded data, the physician can identify the specific electronic signature of the patient's seizure and customize the timing and intensity of the neurostimulation delivered via the device. Once programmed, the device monitors for that electronic signature and delivers the prescribed electrical charge needed to disrupt it and prevent the seizure. Adjustments can be made during office visits to fine tune the timing and intensity of the neurostimulation.

Efficacy and Safety

FDA approval of responsive neurostimulation hinged on the findings of a multicenter, double-blinded, randomized controlled trial (NCT00264810) of the technology in 240 patients (aged 18-70 years) with treatment-refractory partial seizures.[1] To be included in the trial, patients could have no more than two epileptogenic foci (because the device has only two leads), have failed to respond to two antiseizure medications, and have experienced an average of three partial seizures in the past three months. A total of 191 participants were implanted with the device (six of them at MUSC by Dr. Edwards and colleagues) and underwent monitoring to determine seizure signature before being randomized for 12 weeks to either the treatment group (n = 97; device was turned on) or sham group (n =

94; device was not turned on). At the end of the 12 weeks, the trial became open label and the devices were turned on in all patients and data collected for up to two years.

During the 12-week posttransplant period, seizure frequency decreased by 37.9% in the treatment group vs 17.3% in the sham group (p=.012). Seizure frequency was significantly reduced vs baseline in patients in the sham group once they transitioned to the treatment group (p=.04). Overall, 46% of patients receiving responsive neurostimulation during the open-label period achieved a 50% or greater reduction in seizure frequency, and 7.1% were seizure-free.

At 28 days, the rate of serious adverse events was 12% (vs 15% for the prespecified literature-derived comparator), and at 84 days it was 18.3% (vs 36% for the literature-derived comparator). The rates for the two most serious possible adverse events associated with deep brain stimulation were low: four (2.1%) of 191 patients experienced a serious device-related intracerebral hemorrhage, but none sustained permanent neurological damage, and ten (5.2%) of 191 patients developed an infection at the incision site, all confined to the soft tissue and not involving the brain itself.

In meeting both its efficacy and safety endpoints, this trial provides Class I, two-year evidence that responsive neurostimulation can safely prevent partial seizures or decrease their frequency in select patients. A trial to evaluate its efficacy and safety beyond two years is underway, and MUSC is a participating site.

Patient Selection

Surgical resection of the epileptogenic zone remains the most effective treatment for medication-refractory partial seizure epilepsy, and **William A. Vandergrift III, M.D.,** Associate Professor in the Department of Neurosciences, performs many such surgeries at MUSC with excellent results. However, not all patients are interested in or are candidates for surgery. If seizures originate in an "eloquent" area of the brain (ie, one that controls a critical function such as language) or one that would be very difficult to access, resection may not be an option. If the patient has two independent epileptogenic foci and both are in areas that would affect the same function, both cannot be removed without functional loss, and removal of one will not eliminate seizures. For these patients, responsive neurostimulation offers a promising new treatment approach.

An Unexpected Boon

Responsive neurostimulation was expected to offer a number of advantages over resection. Unlike resection, it does not require the sacrifice of any anatomic structures and is reversible (the device can be removed if it does not work). An unexpected boon was its usefulness in helping identify patients who would benefit from resection despite having originally been deemed unsuitable surgical candidates.

Before a patient can undergo resection to control partial seizures, he or she must be evaluated to localize the epileptogenic zone(s). During that evaluation, patients are confined to an epilepsy monitoring suite, where they can be weaned safely from antiseizure medications, undergo a variety of electroencephalographic and imaging studies as well as neuropsychological and other testing, and, if necessary, be implanted with electrodes to help localize the area of the brain that is the source of the seizures. The accuracy of the evaluation may in some cases be affected by the artificiality of this environment, and the cortical recordings made by the responsive neurostimulator while the patient is back at home may reveal new information. One of the MUSC patients enrolled by Dr. Edwards in the trial was found to have two independent foci, ruling out resection. However, when the patient returned home to a more natural environment and resumed his medications, recordings from the responsive neurostimulator revealed that the most disabling symptoms were coming from only one epileptogenic focus, which was removed. The frequency of the patient's seizures decreased markedly more with combined resection and responsive neurostimulation than they had with neurostimulation alone. According to Dr. Edwards, "Responsive neurostimulation does not necessarily preclude resection; in fact, it may actually open up some surgical opportunities for patients—an unexpected benefit of the device."

The Future of Neurostimulation

If moving from one-way to responsive neurostimulation can be likened to the quantum leap forward from the telegraph to the rotary telephone, what advances can we expect as the technology becomes more sophisticated? To imagine the possibilities, Dr. Edwards explains that we need think only of the cell phone: "Think about what a cell phone could do ten years ago compared with what it can do today. Microprocessing is moving forward rapidly, and everything is getting smaller and faster. The microprocessor for the responsive stimulator will become smaller and require less invasive surgery for implantation, and detection and stimulation paradigms will grow by quantum leaps as well," predicts Dr. Edwards.

Reference

[1] Morrell MJ, for the RNS System in Epilepsy Study Group. Responsive cortical stimulation for the treatment of medically intractable partial epilepsy. *Neurology* 2011;77:1295-1304.