Responsive Stimulation in the Management of Medically Refractory Epilepsy

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19.1 Introduction

It is estimated that epilepsy affects 0.6% of people living in developed countries [1] and 1.6% of all people in more rural undeveloped countries. As a result, epilepsy poses a substantial economic burden for health systems across the globe [2]. While the primary first line therapy for treating this disorder is antiepileptic medication, 20% to 30% of patients are unable to gain seizure control with medication alone [3]. In these patients, further medication trials are of very limited utility, and current guidelines recommend referral of these patients to an epilepsy surgery team.

Surgical approaches for the treatment of epilepsy currently include a wide range of techniques that either seek to remove offending epileptogenic tissue or to use electrical stimulation to disrupt or inhibit seizure activity. While these surgical techniques have been shown to yield reproducible and excellent results compared to medication alone [4], epilepsy surgery techniques are vastly underutilized [5]. The best practice for any patient being considered for epilepsy surgery is to be extensively evaluated by a multidisciplinary epilepsy surgery group. These groups specialize in selecting the best therapy for reducing seizure burden while avoiding the excessive risk of permenant neurologic disability [6].

When seizures are localized to an area of the brain in which they can be removed or ablated with an acceptable patient risk, resective or ablative surgery is the best patient option. However, in many circumstances this is not the case. A patient may have multifocal epilepsy such as multilobar epilepsy or bitemporal epilepsy. Alternatively, when the a patient is found to have an epileptic focus located in an eloquent area of the brain, surgical techniques that result in removal or damage to the target area of the brain may be too high risk for the patient. In these circumstances, techniques that employ neurologic stimulation to treat refractory epilepsy are utilized in order to reduce seizure burden while minimizing neurologic deficits.

The three most commonly used chronic neurologic stimulation techniques for medically refractory epilepsy are responsive neurostimulation (RNS), vagal nerve stimulation (VNS), and bilateral deep brain stimulation (DBS) of the anterior nucleus of the thalamus [7]. RNS is an adjunctive epilepsy treatment approved for disabling medically intractable partial-onset seizures in adults who have either one or two seizure foci. These patients also must have completed two or more full antiepileptic medication trials without seizure relief [8, 9]. The treatment provides closed loop stimulation to the epileptogenic regions of the brain when abnormal electrographic activity thought to predict a seizure is detected. The concept, practice, utilization, and evidence for RNS are covered in this chapter.

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19.2 Responsive Neurostimulation: Background

One of the first published studies of RNS in patients covered how stimulation could be used to abort persistent afterdischarges that resulted from cortical stimulation mapping [10]. During cortical stimulation to map function in epilepsy surgery patients, application of another electrical stimulation when an afterdischarge was observed significantly reduced the duration of the afterdischarge. This electrical stimulation was also found to decrease the likelihood of an afterdischarge's evolving into a clinical seizure. In some instances, the afterdischarges halted completely upon application of current (Fig. 19.1). While electrically induced afterdischarges are not physiologically equivalent to preictal spontaneous epileptiform activity, the study's results supported the idea that RNS could be utilized to treat seizures in patients.

This concept was advanced several years later using automated responsive neurostimulation in patients implanted with subdural electrode arrays for seizure localization [11]. An automated algorithm was used to deliver high frequency electrical stimulation to areas of the brain exhibiting seizure-like activity. The outcome of this study was that when patients were receiving local responsive stimulation, their seizure rate dropped by an average of 55%. This work demonstrated that a computer could be programmed to detect ictal precursor activity in the absence of human observation and respond automatically with neurostimulation.

While the previous studies capitalized on patients who already had electrodes implanted during their workup for resective surgery for epilepsy, in 2005 a randomized, double-blind, multicenter, sham-stimulation controlled study was performed to evaluate a device specifically designed to detect and stimulate electrical activity predicted to be an ictal precursor [12]. The RNS device consisted of a combined recording device and neurostimulator implanted into the skull and two leads that served to record for both electrical activity predictive of ictal activity and to stimulate the area in order to abolish the abnormal electrical activity (Fig. 19.2) [9]. These leads have four contacts and can either be cortical strip or depth electrodes. The flexibility of the system is somewhat limited because it only allows recording and stimulating the limited brain areas accessed by the two strip or depth electrodes.

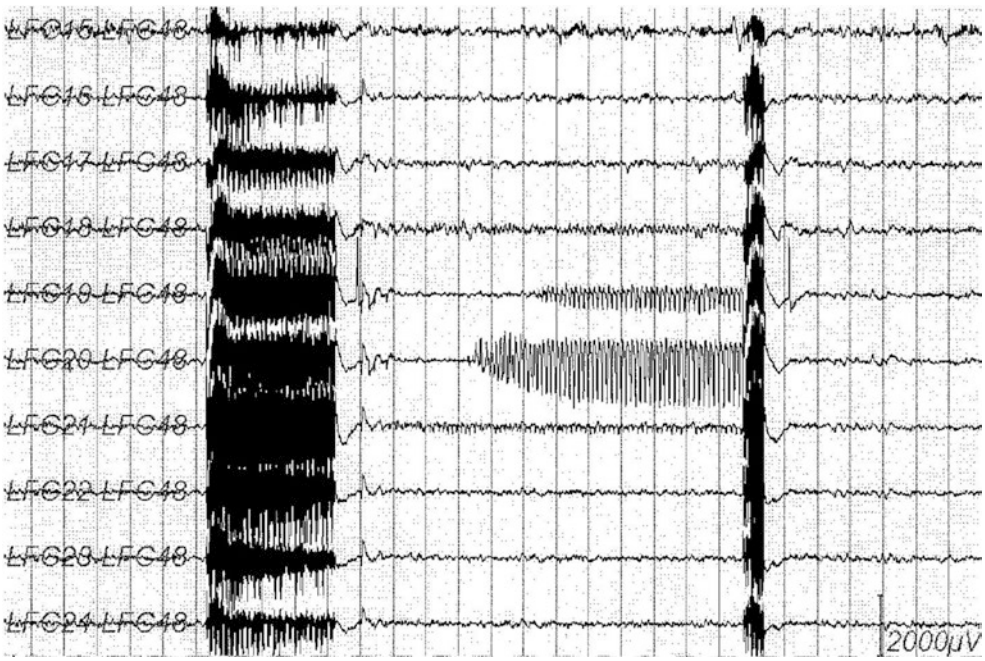

Fig. 19.1 Series of bipolar electrodes showing an afterdischarge (AD) after extraoperative cortical stimulation mapping. In the middle two leads an observable AD is seen. The AD is aborted using an additional short burst of cortical stimulation. (*Adapted from* Lesser et al. [10]; *with permission*.)

In the RNS pivotal trial, 191 adults with medically refractory partial epilepsy and one or two localized seizure foci were implanted with the device. The patients were randomized to receive responsive or sham stimulation. Patients in the treatment group received a 0.5 mA stimulation at 200 Hz for 100 ms when the device detected seizure type activity. The blinded phase continued until 5 months after implant, when all patients entered the open label phase of the experiment and had their devices activated. At the end of the blinded phase, there was a statistically significant reduction in seizure frequency in the stimulation group compared to the sham group. The stimulation group demonstrated a 37.9% reduction in seizure frequency, while the sham group demonstrated a reduction of only 17.3%. During the open label period, once practitioners were able to tailor the parameters used for detection and stimulation, the median reduction in seizure frequency increased to 44% at 1 year, 53% at 2 years, and 66% at 6 years [13, 14]. Notably, these patients achieved a reduction in seizure frequency without any deterioration in neuropsychological function, and most patients had a meaningful increase in quality of life metrics [8, 15].

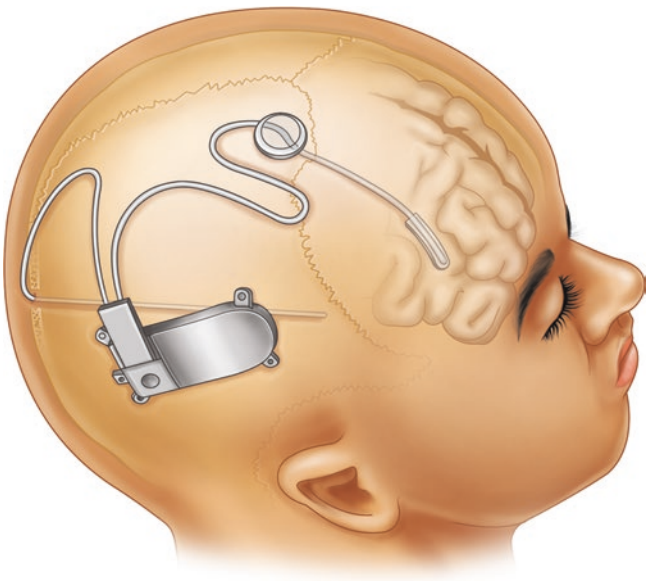

Fig. 19.2 Diagram depicting the neuropace device. The neurostimulator is hooked up to both a depth lead and a strip lead. The depth lead has been inserted through a posterior burr hole deep to the hippocampus, while the strip lead has been placed through a burr hole on a gyrus of the frontal lobe

19.3 Patient Selection

The clinical pathway for selecting a patient to receive RNS for epilepsy is similar to that for any patient undergoing an epilepsy surgery workup. First, patients with medication-resistant epilepsy are referred to a clinical epilepsy neurology group for assessment, characterization of seizure semiology, and assurance that conservative management has been tried and failed. Noninvasive techniques are then used in an attempt to localize the seizure focus. Scalp electroencephalography (EEG) can often provide information about the approximate area and side of the seizure focus. Magnetic resonance imaging (MRI) can demonstrate discrete lesions such as hippocampal sclerosis seen in mesial temporal lobe epilepsy (MTLE), subtle gray and white matter changes in focal cortical dysplasia (FCD), tumors, or vascular malformations. Additional techniques that can be utilized depending on their availability include ictal or interictal single photon emission computed tomography (SPECT), magnetoencephalography (MEG) [16], and computational algorithms for detecting subtle abnormalities on MRI studies initially read as negative [17].

Frequently, the noninvasive workup is insufficient to determine the exact seizure focus. In these cases, invasive surgical monitoring is used to localize the seizure onset zone and guide further treatment. Subdural electrode arrays are implanted via a craniotomy or EEG depth electrodes (Stereo EEG = SEEG) are stereotactically placed in the area(s) of putative seizure onset based on the patient's seizure semiology, imaging results, and scalp EEG findings. Which type of implant is placed depends on the brain area to be evaluated; the possible need for functional mapping; and the epilepsy surgery center's preference and experience. After implantation, the electrodes are monitored extraoperatively for epileptiform interictal spiking and for seizure onset and propagation. These techniques have the advantage of significantly improved spatial and temporal resolution compared to a scalp EEG, given their direct placement on the cortical surface or through the brain parenchyma.

After determining the putative seizure onset zone, selection of the best treatment modality for a patient should be a multidisciplanary discussion that includes the epilepsy neurologist, the neurosurgeon, the neurospsychologist, and most importantly the patient. Removal of the pathologic tissue by means of resection or ablation has been shown to produce

superior seizure freedom rates compared to stimulation-based therapies [17]; however, there are many areas of the brain that will produce either a meaningful or severe neurologic deficit if removed. In those patients in whom the potential for seizure freedom is thought to be outweighed by the potential neurologic deficit, neurostimulation devices can provide the greatest benefit.

Other considerations to be evaluated on a patient-specific basis include the need for future MRIs, the existence of other stimulation devices, the patient's immunologic function, and the patient's social support system [9]. The Neuropace RNS device is currently not MRI compatible, and patients who require frequent MRIs such as those with multiple sclerosis may be poor candidates for RNS. The device also is technically contraindicated for anyone with another device delivering stimulation to the brain, which may make it a poor option for a patient who may also be considering deep brain stimulation for another indication. Also, like all implantable intracranial devices, a serious infection of the device and surrounding tissues including brain, skull, and/or scalp may warrant its removal and treatment of the infection with antibiotics. For patients with immunologic deficiencies, careful consideration should be given to the increased chance for infection. Last, patients are required to frequently upload their seizure information to a central database and must come in for many follow-up visits to fine tune their devices. Unfortunately, patients who are poorly adherent to recommended therapies or do not have a strong social structure to support them may be poor candidates for the device.

19.4 Implantation

Implantation of the device consists of placing strip and/or depth leads and the neurostimulator. The exact surgical procedure varies based on the patient's specific configuration. For patients with depth leads, such as placement into the bilateral hippocampi, the lead placement trajectory is planned on stereotactic software prior to surgery. On the day of surgery, the patient is placed into a stereotactic headframe after being given general anesthesia. A volumetric CT is then acquired and fused to an MRI performed prior to the day of surgery. After image fusion, the patient is placed on the operating room table, with the stereotactic frame base ring fixed to a Mayfield holder. The head is prepped and draped in the usual fashion, bilateral burr holes are made down to the dura, and hemostasis is obtained. After drilling the burr hole, a small trough the width of the lead is made through the side of the burr hole, and a single small "dog bone" titanium plate is affixed with one screw adjacent to the trough for subsequent electrode anchoring. The dura is then incised, hemostasis is achieved, and the depth leads are bilaterally implanted based on the stereotactic coordinates of the trajectories planned on the navigation software. Cannulas that can accommodate a standard 3387 Medtronic lead of 1.27 mm in width can also be used to place the Neuropace lead owing to its similar width of 1.29 mm. After withdrawing the cannula, the depth lead is secured through the trough under the dog bone in order to hold the lead in place and reduce the stress on the lead wire. After securing the electrode, the lead is passed under the skin to the area where the neurostimulator will be implanted. Of note, depending on surgeon preference, frameless stereotaxis or robotic guidance can be used to place the depth electrodes. However, we prefer using a frame-based stereotactic system because of the ease of stereotactic planning and the accuracy of electrode placement.

For strip placement, in almost all instances a previous surgery has been performed for surgical epilepsy localization. In this instance, the patient is placed in a Mayfield clamp, and an incision is made to access the previous craniotomy site. The craniotomy, or a portion of it, is removed, the dura is carefully reopened taking care to carefully dissect the dura from the pia (which may be scarred from the prior surgery), and the strip(s) are slid into position. The dura is then closed, and the craniotomy is replaced. If the strip is not adjacent to the area where the neurostimulator will be placed, the lead is once again passed under the skin to the planned area, and the incision is closed.

For placement of the neurostimulator, the area where the device will be implanted should be toward the back of the head so that the incision and device will be completely obscured by the patient's hair; however, it should not be at a weight-bearing pressure point on the back of the head. The most common location for the implant is the parietal convexity of the skull. A horseshoe incision is made in the scalp large enough to provide

at least 1 cm in all directions around the implant. It is oriented so that the leads do not traverse the incision. Fashioning an incision such that the implant and leads do not lay directly under the incision decreases the chance of infection, wound breakdown, and lead disruption during future device replacements. Following incision and hemostasis, the leads are pulled under the scalp into the area of the incision and wrapped in a moist sponge away from the area to be drilled. Next, the Neuropace ferrule is placed on the surface of the skull, and a marker is used to outline the exact area to be drill. A craniectomy is then drilled and removed in the shape of the ferrule, taking care not to traumatize the underlying dura. Bone wax is used to smooth the edges, and meticulous hemostatsis is performed along with copious irrigation to remove all bone dust from the field. Epidural tenting sutures are placed to minimize the risk of a postoperative epidural hematoma. A partial-thickness craniectomy may be used if the skull is thick enough, minimizing the risk of dural injury or irritation or epidural bleeding. The ferrule is affixed to the skull with four screws provided in the Neuropace kit (Fig. 19.3a). The leads are then passed into the Neuropace stimulator, and the stimulator is affixed to the ferrule (Fig. 19.3b). At this point, we apply a vancomycin powder slurry to decrease the risk of infection, and the incision is closed over the stimulator. The programmer is then draped in a sterile camera sleeve to interrogate the device. Interrogation at this point ensures that the device can be properly accessed through the skin and allows measurement of the impedences of each electrode. Abnormal impedences are greater than 3500 ohms and less than 250 ohms. A CT scan and anteroposterior/lateral x-ray should be obtained postoperatively to document placement (Fig. 19.4).

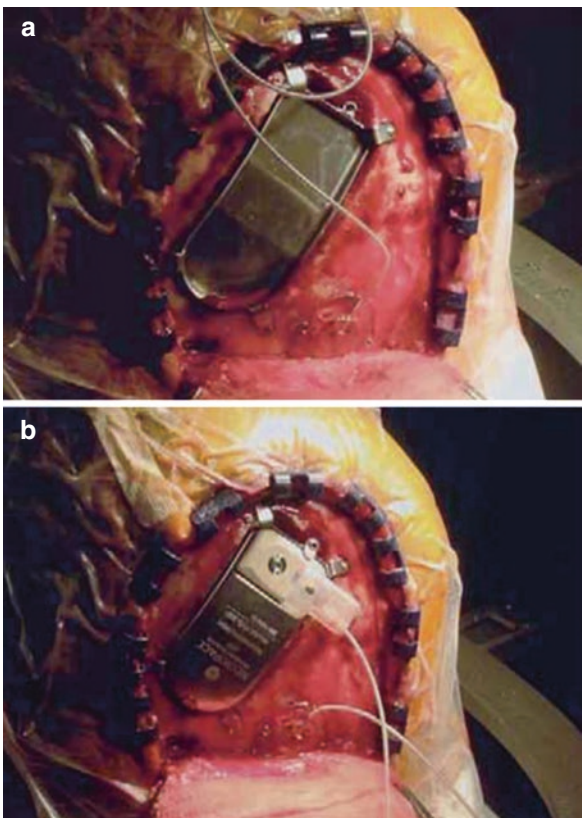

Fig. 19.3 Figure showing the ferrule and the neurostimulator. In part (**a**) the empty ferrule has been placed into the craniectomy site. The craniectomy was made in the same shape as the ferrule to ensure snug placement of the device. In (**b**) the neurostimulator has been placed into the ferrule, and a lead has been inserted into the device. (*Adapted from* Fountas et al. [18]; *with permission*.)

As mentioned previously, the careful planning of each surgical step is imperative and may vary from case to case. In the instance of two depth electrodes, the leads may first be placed with a stereotactic frame and then the frame can be removed. The craniectomy can be performed with the head ring on provided that the ring was placed low enough. If the patient will have two strips implanted, a Mayfield head clamp may be utilized instead without the need for precise stereotactic coordinates. Additionally, if the burr hole or craniotomy incision can be incorporated into the neurostimulator incision area, the incision can be tailored to accommodate both so that fewer incisions are required.

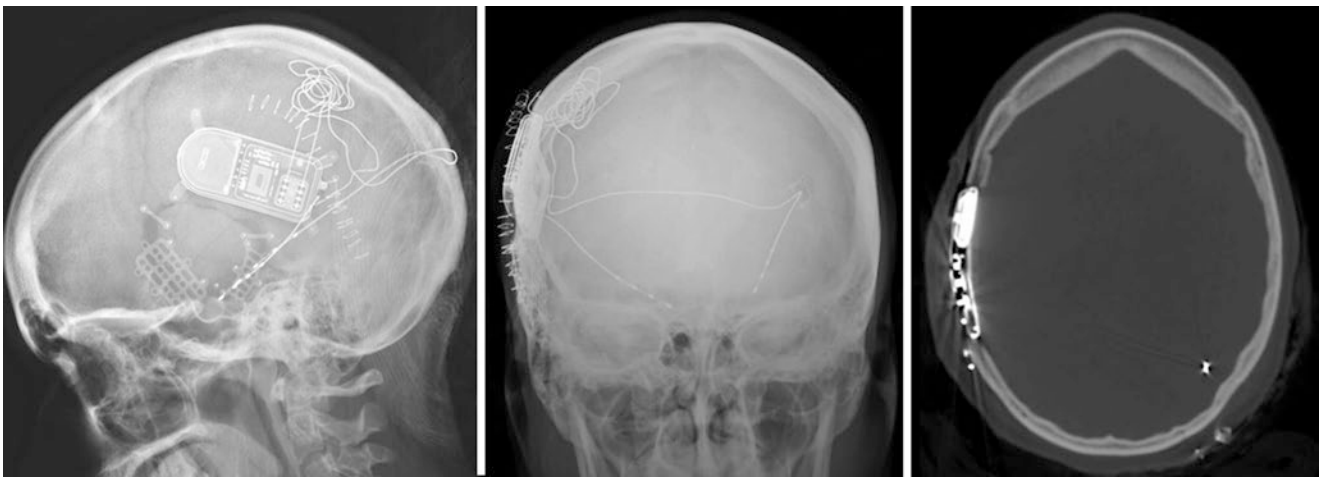

Fig. 19.4 Figure showing plain films and CT scans of an implanted responsive neurostimulator. This patient has bilateral onset mesial temporal lobe seizures and was implanted with bilateral depth electrodes in the parahippocampal region. CT shows the craniectomy and how the ferrule sits within the skull

19.5 Programming of the Device

After implantation in the operating room, the device is usually set to record only. When the device detects specific electrocorticographic patterns, it stores the recording for a set amount of time. There are three ways the device can detect patterns of interest: line length, area, and band pass. Line length is a measure of point-to-point change that is sensitive to both signal amplitude and frequency. As the most globally sensitive of the three methods, it is the recommended initial setting. Area detection is most sensitive to power changes, while bandpass detection is most sensitive to rhythmic and spiking activity. If the patient's seizures were well characterized during the intracranial monitoring evaluation, more specific parameters can be chosen during the placement of the device. Most importantly though, the patient should be counseled on how to store and upload Neuropace information on a daily basis, so that during their first postoperative appointment the information can be used to initiate responsive therapy.

At each follow-up appointment the clinician should first evaluate if ictal events are being captured properly. This can be assessed by comparing the recorded data to patient seizure journals. Of note, continuous ambulatory recording can often reveal that the patient suffers from more frequent electrographic events than are reported in the seizure journals. The detection settings should be changed so that no preictal candidate events are missed. Once the device has been programmed to be sufficiently sensitive to these events, further sessions can be used to carefully tailor the settings to be more specific.

The initial settings for responsive therapy should be left at their default values during the first programming session, and the stimulation should be delivered to the area from which the activity of interest is observed. The default settings are recommended for the initial stimulation phase to allow for a baseline assessment of their effectiveness. After the initial programming phase, 3-month interval visits should be scheduled to better tailor the stimulation to the patient. If the stimulation is not sufficient to abort preictal activity, the initial recommended change is to increase the amplitude of the stimulation by 0.5-mA increments. After changing the current, the stimulation should be trialed in the office to ensure that the stimulation is tolerated by the patient and that it does not induce afterdischarges. If the new stimulation produces a noticeable irritation in the patient, the burst duration can be increased instead of the amplitude.

19.6 Complications and Avoidance

While RNS has a better adverse event profile than resective or ablative surgery, the act of surgical implantation itself still carries a risk. Not including pain and seizure-related complications, the most common adverse events in the pivotal trial were device lead damage, infection, and depression [19]. In approximately 2.6% of patients, the device and/or leads were damaged sometime in the first year. Care must be taken to reduce any potential regions of stress on the device or leads during the implantation in order to decrease the risk of damage. For example, when drilling the burr holes, a trough in the side of the burr hole, as described previously, allows for a more gradual exit from the subdural space and puts less stress on the leads. Sufficient slack should also be placed close to the neurostimulator so that after healing and scarring the lead is not held taut in relation to the neurostimulator.

To decrease infection risk, extra care should be utilized to ensure sterile procedure when prepping and draping. Antibiotic irrigation should be copiously used, and all bone dust should be washed from the field before implantation of any permanent device. We also recommend utilization of vancomycin powder during the implant before closure for additional prophylaxis, and at least one perioperative and postoperative dose of intravenous antibiotics. In the postoperative period, superficial site infections can be treated with antibiotics, but any persistent infection involving the device itself warrants explantation and extended antibacterial therapy. Also, since patients suffering from epilepsy frequently experience comorbid depression, we recommend screening for depression during all postoperative visits [20].

19.7 Limitations and Future Directions

While the RNS device has shown excellent efficacy for reducing seizure frequency in patients with medically refractory epilepsy, the treatment is only able to provide seizure freedom in a very limited number of patients (~10%). Additionally, the therapy is contingent on the ability to localize the ictal focus to one or two specific locations in the brain, a constraint not shared by VNS or anterior thalamic nucleus stimulation. Therefore, while the therapy definitively has a place in the arsenal of treatments for medically refractory epilepsy, it is neither a replacement for resective surgery nor necessarily superior to other electrical stimulation modalities.

Future research will seek to improve the efficacy of the device by utilizing the vast amount of outpatient intracranial recording collected by the RNS device. Research aimed at identifying ideal candidates for responsive neurostimulation and improving seizure detection algorithms will likely improve the efficacy and utility of the RNS device. Additionally, research into preoperative predictors of which candidates will respond best to neurostimulation will naturally improve the device's efficacy. Interestingly, now that hundreds of devices are implanted, we are starting to see that far more epileptic events occur in the human brain than are normally reported. This new vast collection of data can potentially be used to further our understanding of the pathophysiology of epilepsy and allow us to better implement appropriate epilepsy therapies.

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