Brain stimulation for the treatment of epilepsy

JARED FRIDLEY, M.D.,[1] JONATHAN G. THOMAS, M.D.,[1] JOVANY CRUZ NAVARRO, M.D.,[1] AND DANIEL YOSHOR, M.D.[1,2]

[1]Department of Neurosurgery, Baylor College of Medicine; and [2]St. Luke's Neuroscience Center, Houston, Texas

The treatment of patients with refractory epilepsy has always been challenging. Despite the availability of multiple antiepileptic medications and surgical procedures with which to resect seizure foci, there is a subset of epilepsy patients for whom little can be done. Currently available treatment options for these unfortunate patients include vagus nerve stimulation, the ketogenic diet, and electric stimulation, both direct and indirect, of brain nuclei thought to be involved in epileptogenesis. Studies of electrical stimulation of the brain in epilepsy treatment date back to the early 20th century, beginning with research on cerebellar stimulation. The number of potential targets has increased over the years to include the hippocampus, subthalamic nucleus, caudate nucleus, centromedian nucleus, and anterior nucleus of the thalamus (ANT). Recently the results of a large randomized controlled trial, the electrical Stimulation of the Anterior Nucleus of Thalamus for Epilepsy (SANTE) trial, were published, demonstrating a significant reduction in mean seizure frequency with ANT stimulation. Soon after, in 2011, the results of a second randomized, controlled trial—the NeuroPace RNS trial—were published. The RNS trial examined closed-loop, responsive cortical stimulation of seizure foci in patients with refractory partial epilepsy, again finding significant reduction in seizure frequency. In the present review, the authors examine the modern history of electrical stimulation of the brain for the treatment of epilepsy and discuss the results of 2 important, recently published trials, the SANTE and RNS trials.
(http://thejns.org/doi/abs/10.3171/2012.1.FOCUS11334)

KEY WORDS   •   deep brain stimulation   •   epilepsy   •   electrical stimulation

EPILEPSY is a highly prevalent disorder that is a major cause of morbidity in patients throughout the world. Nearly 1% of the population suffers from epilepsy, with an annual incidence of 50/100,000 people.[40] In 60%–70% of epilepsy patients, treatment with antiepileptic medications results in seizure remission.[40] The remaining patients, in whom symptoms are refractory to medications, currently have relatively limited alternative treatment options. Perhaps the most effective option in patients with medically refractory epilepsy is resective epilepsy surgery, which involves the excision of the epileptogenic region of the brain. In patients with well-defined epileptic zones, this can offer a high likelihood of excellent long-term seizure control.[12] In medically intractable patients in whom resection fails to control seizures, or for patients who are not appropriate candidates for surgery, there are a limited number of available palliative options.[21,37,43]

Recently there has been resurgence in interest in the use of brain electrical stimulation for the treatment of patients in whom all else has failed. Multiple deep brain stimulation targets have been studied, including the cerebellum, hippocampus, subthalamic nucleus, caudate nucleus, centromedian nucleus, and anterior nucleus of the thalamus[39] (Fig. 1). Technology itself has also advanced, with the development of responsive cortical stimulation systems that are able to detect seizure activity in real time and deliver direct electrical stimulation to seizure foci in response.[33] In the past year, the results of 2 large randomized, controlled trials have been published: the SANTE (Stimulation of the Anterior Nucleus of Thalamus for Epilepsy)[17] and RNS cortical stimulation trials.[33] In the present article, we review the current and future applications of electrical stimulation for the treatment of epilepsy, including the recent results of the SANTE and RNS trials.

Vagus Nerve Stimulation

In 1997, the US FDA–approved left-sided VNS for the treatment of medically refractory partial epilepsy (Fig. 2). Vagus nerve stimulation has been by far the most
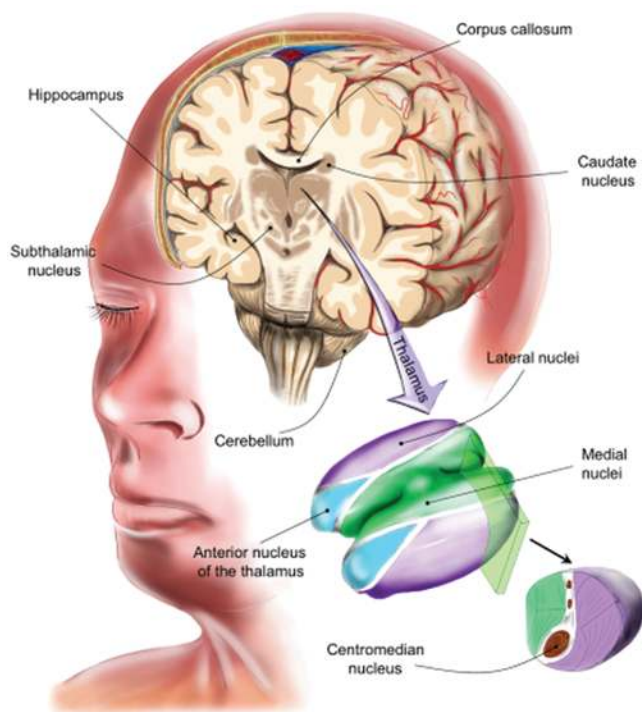

Abbreviations used in this paper: ANT = anterior nucleus of the thalamus; DBS = deep brain stimulation; EEG = electroencephalography; STN = subthalamic nucleus; TLE = temporal lobe epilepsy; VNS = vagus nerve stimulation.

Fig. 1. Illustration demonstrating DBS targets that have been previously studied including the cerebellum, hippocampus, STN, caudate nucleus, CMN, and ANT.

prevalent method of stimulation to treat epilepsy, with more than 60,000 patients having received the implant.[15] It is presumed that stimulation of the vagus nerve results in alterations of activity in the brain, resulting in turn in a decrease in seizures. The mechanism of neuromodulation remains unclear, but it is thought that afferent signaling from the stimulated vagus nerve results in EEG desynchronization.[6,22,26]

There have been 2 randomized double-blind trials demonstrating the efficacy of VNS. In 1994, Ben-Menachem et al.[2] enrolled 114 patients with medically refractory partial epilepsy into a multicenter trial of VNS. After implantation of the stimulator, patients were randomized to receive high-frequency (treatment) or low-frequency (sham) stimulation. Three months after surgery, the investigators found a significant seizure reduction of 25% in the treatment group compared with 6% in the sham group (p = 0.072). A second multicenter randomized blinded trial by Handforth et al.[21] similarly randomized 196 patients (age range 13–65 years) to high- and low-frequency stimulation groups and measured seizure frequency over a 3-month period. They found that patients in the high-stimulation group had an average 28% seizure burden reduction compared with a 15% reduction in the low-stimulation group (p = 0.04). Although the Class I evidence supports the use of VNS only in adults and adolescents with medically refractory partial epilepsy, a recent meta-analysis[16] of Class II and III clinical studies suggests similar efficacy in children (55% reduction in seizures), as well as benefit in patients with generalized epilepsy (58% reduction in seizures). The role of VNS in palliating seizure burden appears to be expanding, although further randomized, blinded, and controlled studies are needed to confirm its efficacy with broader applications.

Deep Brain Stimulation Targets for Treatment of Epilepsy

Cerebellum

Interest in stimulating the cerebellum for epilepsy treatment began in 1941, when Moruzzi,[34] followed by Cooke and Snider,[9] discovered that electrical stimulation of the cerebellum can modify or even halt cortically induced seizures. In 1955, Iwata and Snider[24] studied hippocampal epilepsy and similarly found that cerebellar stimulation resulted in termination of induced hippocampal seizures. These findings led to animal studies of cerebellar stimulation involving various animals, seizure induction methods, stimulation parameters, and electrode locations. However, these initial studies yielded mixed results, with seizure termination not achieved in several studies.[19] The results from these early studies, including the absence of significant adverse effects, led to additional research into cerebellar stimulation in patients with medically refractory epilepsy.

After numerous small clinical studies that produced promising results,[19] Van Buren et al.[45] performed the first double-blind crossover study of 5 patients with medically intractable seizures in whom electrodes were placed on the superior surface of the cerebellum. The patients had a variety of partial and generalized seizures, with focal and/or bilaterally synchronous epileptiform discharges on EEG. In the 15–21 months following implantation of the electrodes, seizure frequency was evaluated in the hospital during three or four 4- to 6-week hospital admissions, during which 7-day periods of alternating on-and-off stimulation were used. No significant differences in seizure frequency were found between intervals. Three of the 5 patients suffered postoperative CSF leakage from the wound. Following this study, Wright et al.[56] performed a double-blind study of 12 patients with medically intractable epilepsy of various origins and clinical patterns. Stimulators were placed on the upper surface of the cerebellum, 2 cm from the midline, through suboccipital bur holes. Patients were allocated to 1 of 3 phases, lasting 2 months each, for a total of 6 months: 1) continuous stimulation alternating from one cerebellar hemisphere to the other every minute, 2) stimulation of both cerebellar hemispheres when activated by the patient, and 3) no stimulation. Data were reported for 11 of the 12 patients, and no differences in seizure frequency or severity during the stimulation periods were noted. Complications included electrode migration in 25% of the cases, wound infection in 16.6%, and mechanical failure in 8.3%. The lack of positive findings from these 2 studies ran contrary to previous clinical studies and tempered enthusiasm for this treatment.

Following the important technological advances in brain stimulation technology since the early studies of cerebellar stimulation, including the introduction of DBS systems for various diseases, Velasco et al.[48] reevaluated cerebellar stimulation for epilepsy with a randomized double-blind pilot study in 2005. They studied 5 patients with medically intractable epilepsy in whom bilateral
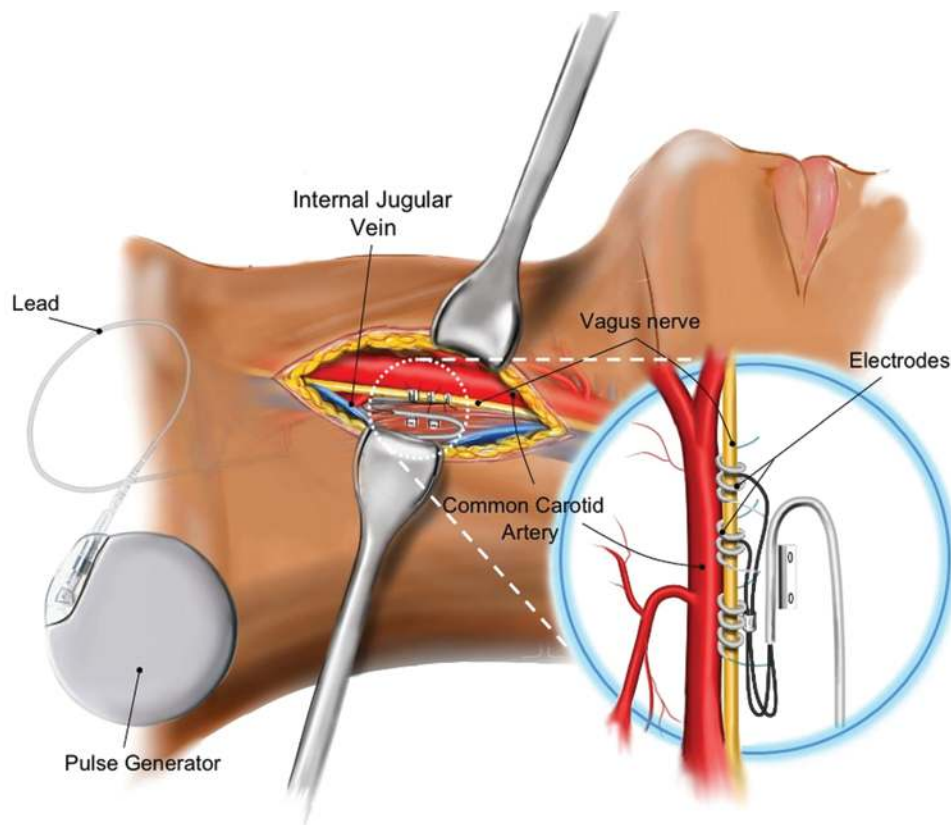
Fig. 2. Neck dissection illustrating a VNS system. There are 3 leads wrapped around the vagus nerve in a helical fashion that are connected to an implanted generator. The generator sends electrical activity to the leads that affect vagus nerve afferent fibers and, through an as-of-yet unknown mechanism, decreases the frequency of seizures in patients with partial-onset epilepsy.

4-contact plate electrodes were placed on the superomedial surface of the cerebellum through 2 suboccipital bur holes. Seizure frequency during the 3-month preimplantation phase was recorded, and postimplantation there was a 1-month sham period in which all stimulators were turned off. Thereafter, a 3-month double-blind trial began in which 3 patients received stimulation and 2 did not. After this period, seizure frequency was measured over a 6-month period during which all stimulators were turned on. Despite the small number of patients, the investigators found a significant reduction ($p = 0.023$) in generalized tonic-clonic and tonic seizure frequency. The 3 patients with stimulators turned on during the double-blind portion had a 33% reduction in seizures, compared with no change in seizure frequency in those patients with the stimulators off. During the 6-month stimulation-on period for all individuals, a mean 41% seizure rate reduction was reported. Complications included electrode migration in 3 patients (60%) and wound infection in 1 (20%).

The mechanism of antiepileptic effects of cerebellar stimulation remains unclear. Initially, it was proposed that stimulation of Purkinje cells resulted in inhibitory output from the cerebellum to the thalamocortical projections. However, histopathological study of cerebellar specimens in epilepsy patients have shown a decrease in Purkinje cell counts,[10,45] and some animal studies have suggested that stimulation inhibits, rather than excites, the Purkinje cells adjacent to the electrodes.[13,36]

Despite conflicting results from the animal studies and clinical trials, there remains considerable interest in cerebellar stimulation for the treatment of medically intractable epilepsy pending further clarification of the more precise target of stimulation and the appropriate stimulator frequency. The results of the pilot study reported by Velasco et al.[46] indicate that further clinical studies involving larger number of patients may be warranted.

Hippocampus

Patients with medically intractable mesial TLE routinely undergo surgical workups to determine if they are appropriate candidates for anteromesial temporal lobectomy[14] or selective amygdalohippocampectomy.[54] However, patients with bilateral mesial TLE, or those with unilateral mesial TLE involving a dominant hippocampus that is essential for adequate memory function, may not be candidates for resection. Moreover, although resection in TLE has proven effective, not all patients experience full relief of seizure burden, and resection is associated with small, but not trivial, risk of a new neurological deficit.[14] For these reasons, there has been interest in targeting the hippocampus for stimulation to treat mesial TLE. The potential advantages of stimulation over anteromesial temporal lobe resection include the reversibility of stimulation, as well as a theoretically decreased risk of inducing memory, language, and visual deficits. The postulated mechanism for the effect of hippocampal stimulation re-

mains unclear, but some have suggested that activation of the perforant pathways results in polysynaptic inhibition of the epileptogenic neurons residing in CA1–4.[50]

Velasco et al.[50] have explored the use of hippocampal stimulation in the treatment of mesial TLE in patients in whom subdural or depth electrodes were implanted to determine seizure foci before a temporal lobectomy. In the study period of 2–3 weeks during which antiepileptic drugs were discontinued, the authors found that in 7 patients who received continuous stimulation of the hippocampal formation or gyrus, no clinical seizures were noted; furthermore, the number of interictal EEG spikes recorded from the hippocampal foci was overall decreased by 60% after 5–6 days. Further studies by Vonck et al.,[53] and again by Velasco et al.,[47] supported these findings. Tellez-Zenteno and colleagues[44] performed a small double-blinded randomized crossover trial in 4 patients with unilateral mesial TLE in whom resection was contraindicated due to risks to memory. In each patient, 1 electrode was placed along the longitudinal axis of the affected hippocampus, via a posterior bur hole. Patients underwent randomized 1-month on- or off-stimulation periods over 6 months, during which blinded investigators measured seizure frequency and performed neuropsychological testing. The investigators found that stimulation produced a median reduction of seizures of 15%, but this percentage did not reach significance in the study sample. There was no difference in secondary outcomes, with stimulation compared with no stimulation, in terms of quality of life, mood, and seizure severity. A second small, double-blind randomized crossover study of bilateral mesial TLE in just 2 patients[31] also failed to replicate the promising results of the earlier nonblinded clinical studies. In this study, bilateral electrodes were placed along the axis of the hippocampus. Following a 3-month baseline period, patients underwent randomized 3-month periods of receiving stimulation or not receiving stimulation while blinded investigators measured seizure frequency and neuropsychological outcomes. The investigators found a 33% reduction in seizures during the on-stimulation phase compared with the off phase.

Randomized controlled double-blind trials of a larger number of patients are needed to better clarify the role, if any, of hippocampal stimulation in the treatment of TLE. Currently, the METTLE (http://clinicaltrials.gov/ct2/show/NCT00717431) and the CoRaStir (http://clinicaltrials.gov/ct2/show/NCT00431457) randomized controlled trials are among the those underway to clarify the role of this treatment modality.[25] The METTLE trial is a multicenter parallel-group double-blind randomized controlled trial enrolling adults with uni- or bilateral mesial TLE, including those who may be candidates for resection and those who are not. These patients undergo hippocampal electrode implantation and are randomized to a stimulation or no-stimulation group. At the end of a 7-month follow-up period and outcome assessment, patients are then offered electrode removal, surgical therapy, or medical therapy based on best evidence. Primary and secondary outcomes will include seizure frequency, cognition, mood, and quality of life. The CoRaStir trial will randomize adults with TLE into 1 of 3 treatment arms: amygdalohippocampectomy, hippocampal electrode with stimulation, or hippocampal electrode without stimulation. Investigators will report outcomes in seizure frequency, neuropsychological testing, and quality of life.[25]

Subthalamic Nucleus

The role of the basal ganglia in epilepsy has been previously explored in a number of experiments. Injection of γ-butyric-acid agonists and lesioning of the substantia nigra suppress seizure activity in many animal models of epilepsy.[20] The STN has glutamatergic efferents to the substantia nigra and modulates its inhibitory output. This anatomical property, coupled with the growth of experience with STN DBS in diseases such as Parkinson disease, led Vercueil et al.[51] to perform STN DBS in a rat model of epilepsy. Bilateral high-frequency STN DBS was found to suppress ongoing spontaneous absence seizures in rats and suggested its clinical application in humans.

In 2001 Benabid et al.[3] were the first to report a series of 3 patients with medication refractory epilepsy who were implanted with STN DBS. One patient had focal cortical dysplasia, the second had myoclonic epilepsy, and the third (in whom surgical therapy failed) had bilateral frontal epilepsy. All 3 patients were reported to have significant reduction in seizure frequency with stimulation, 83% and 50% in the first 2 patients. The percentage of reduction in the third patient was not reported.

Since then several studies of patients have demonstrated mixed results from STN DBS for epilepsy.[4,5,41,52,55] Chabardès et al.[5] reported a series of 5 patients with different epilepsy subtypes treated with STN stimulation. Three patients had partial seizures and had a 67%–80% reduction in seizure frequency, whereas the others, 1 with myoclonic epilepsy and 1 with Dravet syndrome, witnessed little to no improvement. In a recent series of 5 patients with refractory myoclonic epilepsy,[55] STN/substantia nigra DBS resulted in a 30%–100% reduction in seizure frequency in all patients. Interestingly, 4 of the 5 patients had an additional set of electrodes implanted in the ventral intermediate nucleus, but stimulation there failed to produce any therapeutic effect. The published clinical reports indicate that STN DBS may be a promising therapeutic target in patients with certain forms of epilepsy, but both larger series and more rigorous clinical trials are needed to determine the role of STN DBS in epilepsy.

Caudate Nucleus

The role of the caudate nucleus in modulation of seizure activity has been suggested by animal studies demonstrating reduced hippocampal spike frequency and amplitude with caudate stimulation.[28] In several series of patients reported by Sramka and associates[42] and Chkhenkeli and collaborators,[7,8] stimulation of the caudate nucleus was performed for treatment-resistant epilepsy. In a 1997 study of 38 patients, Chkhenkeli and Chkhenkeli[7] showed that low-frequency stimulation (4–6 Hz) led to a decrease in interparoxysmal activity and focal discharges in the neocortical and medial temporal epileptic foci, as well as abrupt cessation of spreading and generalized discharges. Later, in 2004, Chkhenkeli and colleagues[8] showed that low-frequency caudate stimula-

tion reduced the frequency of generalized, complex, and secondary generalized seizures and suppressed subclinical epileptic afterdischarges. More studies are needed to determine if the caudate nucleus represents a viable epilepsy DBS target.

Centromedian Nucleus

The CMN is thought to help regulate structures involved in the genesis of generalized seizures through widespread connections to various cortical areas including mesial temporal lobe structures.[32] In 1987 Velasco et al.[49] reported on a series of 5 patients with generalized or multifocal refractory seizures who underwent bilateral CMN DBS. They found a substantial reduction in the frequency of seizures, both clinically and on EEG. A follow-up study in 2006[46] of 13 patients with Lennox-Gastaut syndrome showed an overall seizure frequency reduction of 80% at 18 months postimplantation, significant functional improvement, and no reported side effects. The most severely affected patients seemed to respond the most to stimulation.

Fisher et al.[18] performed a double-blind crossover pilot study of CMN stimulation in 7 patients with intractable epilepsy. The patients underwent 3 month-long periods with or without stimulation and a 3-month washout period in between. There was a 30% mean reduction in frequency of generalized tonic-clonic seizures when the stimulator was on compared with a decrease of 8% when it was off. There were no reported treatment side effects. Treatment differences were not significant.

Anterior Nucleus of the Thalamus

The ANT represents an attractive stimulation target due to its widespread thalamocortical projections. Early studies in both animal models of epilepsy[27] and in humans with refractory epilepsy[35] had demonstrated that lesioning of the ANT can decrease seizure frequency and duration. It was not until after the advent of DBS that the first human ANT DBS for epilepsy study was published in 1980 by Cooper et al.[11] In 2002, Hodaie et al.[23] published the results of a series of 5 patients with medically refractory epilepsy who underwent bilateral ANT electrode placement. There was an overall mean seizure reduction of greater than 50%. However, the decrease in seizure frequency began immediately after electrode implantation and before stimulation began. It was therefore not clear whether the seizure reduction was due to the implantation of the electrodes themselves or because of stimulation or both. Subsequent published studies of small series of patients with ANT implants showed similar results.[1,29,30,38]

In 2010 the highly anticipated results of the SANTE trial were published.[17] The SANTE trial was the first large, multicenter, double-blind, randomized trial that examined the effects of ANT DBS in patients with intractable epilepsy. A total of 110 patients underwent bilateral electrode implantations in the ANT. One month after implantation, the patients were then randomized to either a stimulation group or a no-stimulation group for a 3-month "blinded" phase. This was followed by a 9-month open-label phase in which all patients had their stimulators turned on and stimulation parameters were optimized to minimize adverse events. Long-term follow-up was achieved in 99 patients at 13 months and 81 patients at 25 months. The primary outcome assessed was monthly seizure rate. Secondary outcomes included the Liverpool Seizure Severity Scale, Quality of Life in Epilepsy Scale, and neuropsychological assessment.

At the end of the 3-month blinded phase, there was a 40.4% decrease in median seizure frequency in the stimulated group compared with a 14.5% decrease in the control no-stimulation group (p = 0.0017). That the control group also had a decrease in seizure frequency is consistent with studies mentioned previously showing an implantation effect. This effect alone, however, does not explain the significant difference between the stimulation and control group and suggests stimulation did indeed have an effect. Interestingly, patients with seizures originating from one or both temporal lobes had a significant difference in median seizure reduction in the stimulation group compared with the control group (44.2% and 21.8%, respectively; p = 0.025), while patients with seizures originating from the frontal, parietal, or occipital lobe did not.

During the long-term follow-up there was a 41% decrease in median seizure frequency at 13 months and 56% decrease at 25 months. Fourteen patients were seizure free for at least 6 months during the entire study. Nine patients had an increase in median seizure frequency at 25 months. The most common adverse event was paresthesias, reported in 18.2% of participants, which tended to occur during the 1st month of implantation. Depression and memory impairment occurred in significantly more people in the stimulation group during the blinded phase (p = 0.0162 and 0.0316, respectively), although most were transient events and resolved during term follow-up.

The SANTE trial demonstrated the overall effectiveness of ANT stimulation as a palliative measure for reducing seizure frequency in patients in whom epilepsy is refractory to medical therapy. In addition, there were 14 patients who were seizure free for at least 6 months during the study period, indicating that some patients may benefit from ANT stimulation more than others. Further study of the optimal patient selection criteria for this promising procedure is indicated.

Responsive Stimulation

An important recent development in the ongoing development of brain stimulation as a viable therapy for epilepsy is the advent of "open loop" or responsive cortical stimulation. Traditional DBS involves the use of chronic, continuous stimulation of a target, so-called closed-loop stimulation. Responsive stimulation first involves implantation of subdural or depth electrodes in a brain target area of interest (Fig. 3). The electrodes are then connected to a small device implanted subcutaneously in the individual. Unlike traditional closed-loop systems, the electrodes have both a stimulation and detection function. Electrocorticographic activity at the target is continuously monitored and recorded by the implanted computer. When abnormal electrocorticographic activity is detected, electrical stimulation is delivered with the goal of dis-
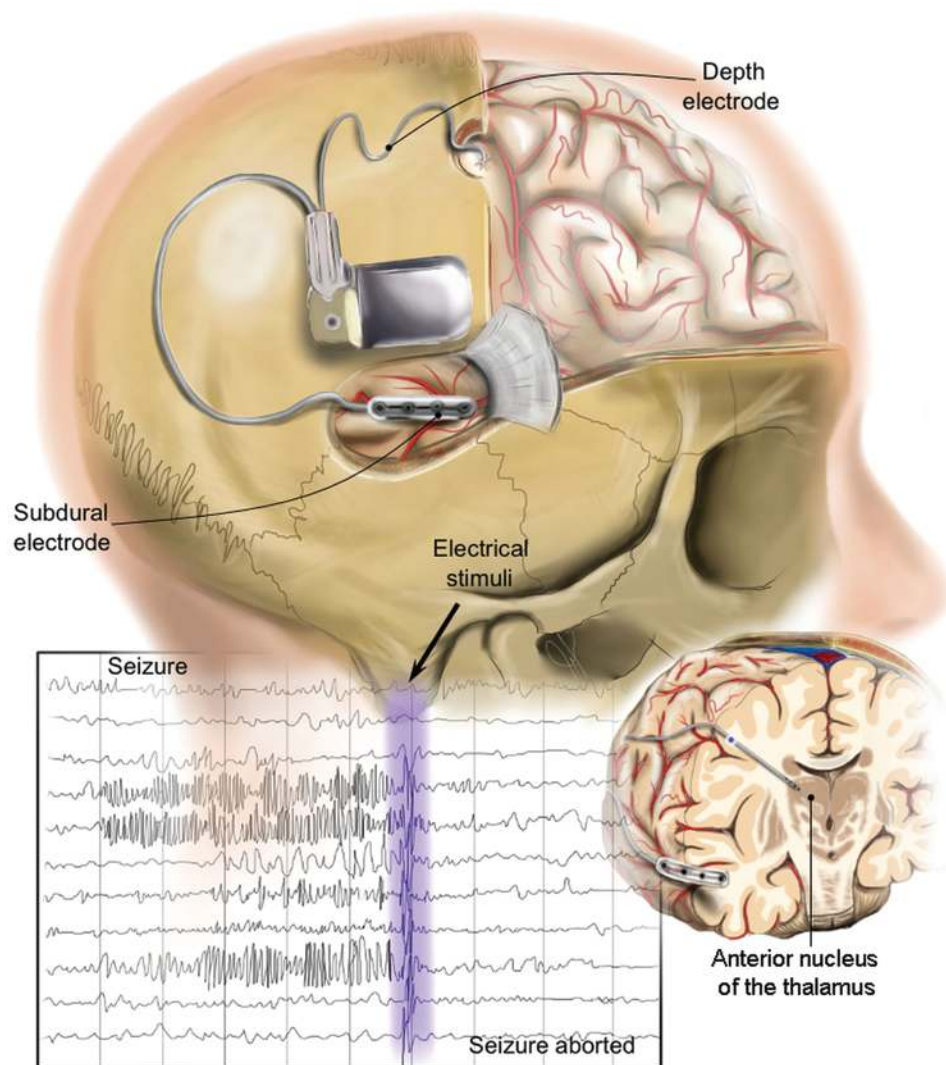
Fɪɢ. 3. Illustration of a responsive or closed-loop stimulation system. Subdural or depth electrodes are implanted into or adjacent to seizure foci. The electrodes are connected to a neurostimulator implanted in the patient's skull. When electrical activity that heralds the onset of a seizure is detected, electrical stimulation is sent to the site of lead implantation, disrupting the abnormal electrical activity and preventing the seizure.

rupting the abnormal activity. Recently, a responsive cortical stimulation system (RNS System, NeuroPace) was studied in a large, multicenter, double-blind, randomized, controlled trial for patients with refractory partial-onset seizures, the results of which were published in 2011.[33]

In 191 adults with refractory partial-onset seizures, either subdural or depth electrodes were implanted at 1 or 2 prespecified seizure foci. The patients were randomized 1 month later into either a sham-stimulation group or a treatment group. There was a 1-month, patient-blinded, postimplantation stimulation optimization period during which the treatment group, but not the sham group, had their stimulators turned on and optimized. Both groups then entered a 3-month blinded evaluation period, in which the treatment group underwent stimulation, but not the sham group. Patients in the sham group then had their stimulators turned on, and all participants entered an open-label period over 84 weeks. The primary end point studied was the difference in mean seizure fre-

quency reduction between the treatment and sham groups compared with their baseline preimplantation seizure frequency. Multiple secondary end points were studied, including neuropsychiatric end points and quality of life measures.

During the 1st month after implantation, there was a decrease in mean seizure frequency in both the sham and treatment groups, similar to the effect seen in the SANTE trial that was attributed to an "implantation effect."[17] Because many patients in the RNS trial solely had subdural electrodes implanted, rather than depth electrodes, it is unlikely that this initial reduction in seizures, in the absence of stimulation, was due to a microlesioning effect. It is possible that there was an initial placebo effect, as the patients all knew they had electrodes implanted. Over the rest of the blinded evaluation period, a difference in seizure reduction in the treatment group compared with the sham group became more apparent, with the treatment group having 27% fewer days with seizures compared

TABLE 1: Large randomized controlled trials of brain stimulation

Authors & Year	No. of Patients	Target	Seizure Frequency Reduction Group	
			Treatment	Sham
Ben-Menachem et al., 1994	114	VNS	25%	6%
Handforth et al., 1998	196	VNS	28%	15%
Fisher et al., 2010	110	ANT	40.4%	14.5% (median)
Morrell et al., 2011	191	direct-seizure foci	37.9%	17.3%

with just a 16% reduction in the sham group (p = 0.048). Over the entire blinded evaluation period, there was a 37.9% reduction in mean seizure frequency in the treatment group compared with a 17.3% reduction in the sham group (p = 0.012). Of 102 patients who were followed up at 2 years during the open-label period, 46% had at least a 50% reduction in their mean seizure frequency. Both sham and treatment groups had similar improvements in secondary outcome measures, including quality of life, at the end of the blinded evaluation period, possibly due to close follow-up and consistent epilepsy care or a placebo effect. However, the treatment group had greater improvements at 1 and 2 years into the open-label period in verbal functioning, visuospatial ability, and memory (p < 0.05). There were no significant differences in adverse events between the groups.

The responsive cortical stimulation trial represents a promising potential approach for the treatment of epilepsy and potentially for other disorders, such as Tourette syndrome, in which practitioners can simultaneously monitor and tailor stimulation parameters to modulate abnormal brain electrical activity. More study of the advantages and disadvantages of open-loop systems is needed.

Conclusions

Electrical stimulation of the brain in the treatment of epilepsy has progressed significantly over the past several decades. Important developments include the completion of rigorous clinical trials (Table 1) testing several different stimulation targets for epilepsy control, as well as advances in brain stimulation technology and hardware, including smart, open-loop systems that deliver stimulation in response to recorded pre-epileptic activity in an attempt to stop seizures before they occur, in real time. Published clinical trials of brain stimulation for epilepsy have been primarily restricted to the subset of patients with medication-refractory epilepsy that is also refractory to, or not deemed appropriate for, treatment with established epilepsy surgery techniques. While statistically significant reductions in seizures have been observed using several different stimulation techniques, including VNS, anterior thalamic stimulation, and RNS, this effect is currently only palliative and does not approach efficacy comparable with that seen with resection in appropriately selected patients. Nonetheless, current limits in the efficacy of antiepileptic medications and epilepsy surgery, combined with the substantial number of patients who continue to suffer from uncontrolled epilepsy, motivate epilepsy researchers to continue to explore brain stimulation as an alternative therapy. The promising results of the aforementioned studies on brain stimulation further drive interest in refining brain stimulation for epilepsy. More research is needed to determine optimal stimulation targets and techniques, as well as to determine which epilepsy patients may benefit the most from this technology.

References

1. Andrade DM, Zumsteg D, Hamani C, Hodaie M, Sarkissian S, Lozano AM, et al: Long-term follow-up of patients with thalamic deep brain stimulation for epilepsy. **Neurology 66:** 1571–1573, 2006
2. Ben-Menachem E, Mañon-Espaillat R, Ristanovic R, Wilder BJ, Stefan H, Mirza W, et al: Vagus nerve stimulation for treatment of partial seizures: 1. A controlled study of effect on seizures. **Epilepsia 35:**616–626, 1994
3. Benabid AL, Koudsie A, Benazzouz A, Vercueil L, Fraix V, Chabardes S, et al: Deep brain stimulation of the corpus luysi (subthalamic nucleus) and other targets in Parkinson's disease. Extension to new indications such as dystonia and epilepsy. **J Neurol 248 Suppl 3:**III37–III47, 2001
4. Capecci M, Ricciuti RA, Ortenzi A, Paggi A, Durazzi V, Rychlicki F, et al: Chronic bilateral subthalamic stimulation after anterior callosotomy in drug-resistant epilepsy: long-term clinical and functional outcome of two cases. **Epilepsy Res** [epub ahead of print], 2011
5. Chabardès S, Kahane P, Minotti L, Koudsie A, Hirsch E, Benabid AL: Deep brain stimulation in epilepsy with particular reference to the subthalamic nucleus. **Epileptic Disord 4 (Suppl 3):**S83–S93, 2002
6. Chase MH, Nakamura Y, Clemente CD, Sterman MB: Afferent vagal stimulation: neurographic correlates of induced EEG synchronization and desynchronization. **Brain Res 5:** 236–249, 1967
7. Chkhenkeli SA, Chkhenkeli IS: Effects of therapeutic stimulation of nucleus caudatus on epileptic electrical activity of brain in patients with intractable epilepsy. **Stereotact Funct Neurosurg 69:**221–224, 1997
8. Chkhenkeli SA, Sramka M, Lortkipanidze GS, Rakviashvili TN, Bregvadze ES, Magalashvili GE, et al: Electrophysiological effects and clinical results of direct brain stimulation for intractable epilepsy. **Clin Neurol Neurosurg 106:**318–329, 2004
9. Cooke PM, Snider RS: Some cerebellar influences on electrically-induced cerebral seizures. **Epilepsia 4:**19–28, 1955

10. Cooper IS, Amin I, Gilman S: The effect of chronic cerebellar stimulation upon epilepsy in man. **Trans Am Neurol Assoc 98:**192–196, 1973

11. Cooper IS, Upton AR, Amin I: Reversibility of chronic neurologic deficits. Some effects of electrical stimulation of the thalamus and internal capsule in man. **Appl Neurophysiol 43:** 244–258, 1980

12. de Tisi J, Bell GS, Peacock JL, McEvoy AW, Harkness WF, Sander JW, et al: The long-term outcome of adult epilepsy surgery, patterns of seizure remission, and relapse: a cohort study. **Lancet 378:**1388–1395, 2011

13. Dow RS, Fernandez-Guardiola A, Manni E: The influence of the cerebellum on experimental epilepsy. **Electroencephalogr Clin Neurophysiol 14:**383–398, 1962

14. Engel J Jr, Wiebe S, French J, Sperling M, Williamson P, Spencer D, et al: Practice parameter: temporal lobe and localized neocortical resections for epilepsy. **Epilepsia 44:**741–751, 2003

15. Englot DJ, Chang EF, Auguste KI: Efficacy of vagus nerve stimulation for epilepsy by patient age, epilepsy duration, and seizure type. **Neurosurg Clin N Am 22:**443–448, v, 2011

16. Englot DJ, Chang EF, Auguste KI: Vagus nerve stimulation for epilepsy: a meta-analysis of efficacy and predictors of response. A review. **J Neurosurg 115:**1248–1255, 2011

17. Fisher R, Salanova V, Witt T, Worth R, Henry T, Gross R, et al: Electrical stimulation of the anterior nucleus of thalamus for treatment of refractory epilepsy. **Epilepsia 51:**899–908, 2010

18. Fisher RS, Uematsu S, Krauss GL, Cysyk BJ, McPherson R, Lesser RP, et al: Placebo-controlled pilot study of centromedian thalamic stimulation in treatment of intractable seizures. **Epilepsia 33:**841–851, 1992

19. Fountas KN, Kapsalaki E, Hadjigeorgiou G: Cerebellar stimulation in the management of medically intractable epilepsy: a systematic and critical review. **Neurosurg Focus 29(2):**E8, 2010

20. Gale K: Subcortical structures and pathways involved in convulsive seizure generation. **J Clin Neurophysiol 9:**264–277, 1992

21. Handforth A, DeGiorgio CM, Schachter SC, Uthman BM, Naritoku DK, Tecoma ES, et al: Vagus nerve stimulation therapy for partial-onset seizures: a randomized active-control trial. **Neurology 51:**48–55, 1998

22. Henry TR: Therapeutic mechanisms of vagus nerve stimulation. **Neurology 59 (6 Suppl 4):**S3–S14, 2002

23. Hodaie M, Wennberg RA, Dostrovsky JO, Lozano AM: Chronic anterior thalamus stimulation for intractable epilepsy. **Epilepsia 43:**603–608, 2002

24. Iwata K, Snider RS: Cerebello-hippocampal influences on the electroencephalogram. **Electroencephalogr Clin Neurophysiol 11:**439–446, 1959

25. Jobst B: Brain stimulation for surgical epilepsy. **Epilepsy Res 89:**154–161, 2010

26. Koo B: EEG changes with vagus nerve stimulation. **J Clin Neurophysiol 18:**434–441, 2001

27. Kusske JA, Ojemann GA, Ward AA Jr: Effects of lesions in ventral anterior thalamus on experimental focal epilepsy. **Exp Neurol 34:**279–290, 1972

28. La Grutta V, Sabatino M: Focal hippocampal epilepsy: effect of caudate stimulation. **Exp Neurol 99:**38–49, 1988

29. Lee KJ, Jang KS, Shon YM: Chronic deep brain stimulation of subthalamic and anterior thalamic nuclei for controlling refractory partial epilepsy. **Acta Neurochir Suppl (Wien) 99:** 87–91, 2006

30. Lim SN, Lee ST, Tsai YT, Chen IA, Tu PH, Chen JL, et al: Electrical stimulation of the anterior nucleus of the thalamus for intractable epilepsy: a long-term follow-up study. **Epilepsia 48:**342–347, 2007

31. McLachlan RS, Pigott S, Tellez-Zenteno JF, Wiebe S, Parrent A: Bilateral hippocampal stimulation for intractable temporal lobe epilepsy: impact on seizures and memory. **Epilepsia 51:**304–307, 2010

32. Miller JW, Ferrendelli JA: The central medial nucleus: thalamic site of seizure regulation. **Brain Res 508:**297–300, 1990

33. Morrell MJ: Responsive cortical stimulation for the treatment of medically intractable partial epilepsy. **Neurology 77:**1295–1304, 2011

34. Moruzzi G: Effects at different frequencies of cerebellar stimulation upon postural tonus and myotatic reflexes. **Electroencephalogr Clin Neurophysiol 2:**463–469, 1950

35. Mullan S, Vailati G, Karasick J, Mailis M: Thalamic lesions for the control of epilepsy. A study of nine cases. **Arch Neurol 16:**277–285, 1967

36. Mutani R, Bergamini L, Doriguzzi T: Experimental evidence for the existence of an extrarhinencephalic control of the activity of the cobalt rhinencephalic epileptogenic focus. Part 2. Effects of the paleocerebellar stimulation. **Epilepsia 10:**351–362, 1969

37. Neal EG, Chaffe H, Schwartz RH, Lawson MS, Edwards N, Fitzsimmons G, et al: The ketogenic diet for the treatment of childhood epilepsy: a randomised controlled trial. **Lancet Neurol 7:**500–506, 2008

38. Osorio I, Overman J, Giftakis J, Wilkinson SB: High frequency thalamic stimulation for inoperable mesial temporal epilepsy. **Epilepsia 48:**1561–1571, 2007

39. Rahman M, Abd-El-Barr MM, Vedam-Mai V, Foote KD, Murad GJ, Okun MS, et al: Disrupting abnormal electrical activity with deep brain stimulation: is epilepsy the next frontier? **Neurosurg Focus 29(2):**E7, 2010

40. Sander JW: The epidemiology of epilepsy revisited. **Curr Opin Neurol 16:**165–170, 2003

41. Shon YM, Lee KJ, Kim HJ, Chung YA, Ahn KJ, Kim YI, et al: Effect of chronic deep brain stimulation of the subthalamic nucleus for frontal lobe epilepsy: subtraction SPECT analysis. **Stereotact Funct Neurosurg 83:**84–90, 2005

42. Sramka M, Fritz G, Gajdosová D, Nádvorník P: Central stimulation treatment of epilepsy. **Acta Neurochir Suppl (Wien) 30:**183–187, 1980

43. Tanriverdi T, Olivier A, Poulin N, Andermann F, Dubeau F: Long-term seizure outcome after corpus callosotomy: a retrospective analysis of 95 patients. Clinical article. **J Neurosurg 110:**332–342, 2009

44. Tellez-Zenteno JF, McLachlan RS, Parrent A, Kubu CS, Wiebe S: Hippocampal electrical stimulation in mesial temporal lobe epilepsy. **Neurology 66:**1490–1494, 2006

45. Van Buren JM, Wood JH, Oakley J, Hambrecht F: Preliminary evaluation of cerebellar stimulation by double-blind stimulation and biological criteria in the treatment of epilepsy. **J Neurosurg 48:**407–416, 1978

46. Velasco AL, Velasco F, Jiménez F, Velasco M, Castro G, Carrillo-Ruiz JD, et al: Neuromodulation of the centromedian thalamic nuclei in the treatment of generalized seizures and the improvement of the quality of life in patients with Lennox-Gastaut syndrome. **Epilepsia 47:**1203–1212, 2006

47. Velasco AL, Velasco F, Velasco M, Trejo D, Castro G, Carrillo-Ruiz JD: Electrical stimulation of the hippocampal epileptic foci for seizure control: a double-blind, long-term follow-up study. **Epilepsia 48:**1895–1903, 2007

48. Velasco F, Carrillo-Ruiz JD, Brito F, Velasco M, Velasco AL, Marquez I, et al: Double-blind, randomized controlled pilot study of bilateral cerebellar stimulation for treatment of intractable motor seizures. **Epilepsia 46:**1071–1081, 2005

49. Velasco F, Velasco M, Ogarrio C, Fanghanel G: Electrical stimulation of the centromedian thalamic nucleus in the treatment of convulsive seizures: a preliminary report. **Epilepsia 28:**421–430, 1987

50. Velasco M, Velasco F, Velasco AL, Boleaga B, Jimenez F, Brito F, et al: Subacute electrical stimulation of the hippocampus blocks intractable temporal lobe seizures and paroxysmal EEG activities. **Epilepsia 41:**158–169, 2000

51. Vercueil L, Benazzouz A, Deransart C, Bressand K, Mares-

caux C, Depaulis A, et al: High-frequency stimulation of the subthalamic nucleus suppresses absence seizures in the rat: comparison with neurotoxic lesions. **Epilepsy Res 31:**39–46, 1998

52. Vesper J, Klostermann F, Stockhammer F, Funk T, Brock M: Results of chronic subthalamic nucleus stimulation for Parkinson's disease: a 1-year follow-up study. **Surg Neurol 57:** 306–313, 2002

53. Vonck K, Boon P, Achten E, De Reuck J, Caemaert J: Long-term amygdalohippocampal stimulation for refractory temporal lobe epilepsy. **Ann Neurol 52:**556–565, 2002

54. Wieser HG, Ortega M, Friedman A, Yonekawa Y: Long-term seizure outcomes following amygdalohippocampectomy. **J Neurosurg 98:**751–763, 2003

55. Wille C, Steinhoff BJ, Altenmüller DM, Staack AM, Bilic S, Nikkah G, et al: Chronic high-frequency deep-brain stimulation in progressive myoclonic epilepsy in adulthood—report of five cases. **Epilepsia 52:**489–496, 2011

56. Wright GD, McLellan DL, Brice JG: A double-blind trial of chronic cerebellar stimulation in twelve patients with severe epilepsy. **J Neurol Neurosurg Psychiatry 47:**769–774, 1984

Address correspondence to: Daniel Yoshor, M.D., Department of Neurosurgery, Baylor College of Medicine, 1709 Dryden, Suite 750, Houston, Texas 77030. email: dyoshor@bcm.tmc.edu.