Deep brain stimulation for medically refractory epilepsy

THOMAS L. ELLIS, M.D., AND ANDREW STEVENS, M.D.

Department of Neurosurgery, Wake Forest University School of Medicine, Winston-Salem, North Carolina

Epilepsy is a chronic neurological disorder that affects 0.5–1% of the population. More than one-third of all patients with epilepsy have incompletely controlled seizures or debilitating side effects in spite of optimal medical management. Medically refractory epilepsy is associated with injury and death, psychosocial dysfunction, and significant cognitive impairment. Treatment options for these patients include new AEDs, which may lead to seizure freedom in 7% of patients and resection, which is associated with long-term seizure freedom in 60–80% of patients. Surgery in patients whose epilepsy has proven refractory to AEDs provides a high likelihood of reduction in seizure frequency, is generally safe, and is recommended in selected patients with refractory partial seizures. In spite of improvements in surgical technique, ~4% of patients will suffer death or permanent neurological disability afterwards. In addition, more than one-third of patients will not be candidates for resection. There are limited options for patients who are not candidates for resection. Neuromodulatory treatment, which consists of electrical pulses administered to neural tissue to modulate its activity, may be an option for these patients. The interest in neuromodulation for neurological disorders is driven by a desire to discover both less invasive surgical treatments and new treatments for patients whose medical conditions remain refractory to existing modalities. Vagal nerve stimulation is a neuromodulatory approach that was developed in the 1980s and is now routinely available. As an adjunct to medical management, vagal nerve stimulation may yield up to a 50% reduction in seizure frequency, although most of these patients will not be completely seizure free. Deep brain stimulation is another example of neuromodulation. Given the significant experience and success of DBS for movement disorders combined with its reversibility, programmability, and low risk of complications, there has been a resurgence of interest in using DBS devices for treating medically refractory epilepsy.

Deep brain stimulation lead implantation within the ANT, as well as other CNS targets—including the CN, centromedian nucleus of the thalamus, cerebellum, hippocampus, and STN—results in seizure reduction in selected patients. The exact mechanism of action of DBS in reducing seizure activity is unknown. It is known that stereotactic lesions of the ANT in humans can result in reduction in seizure frequency. Some evidence suggests that DBS may interfere with synchronized oscillations by neurotransmitter release. Other evidence suggests that the most likely mechanism may involve stimulation-induced modulation of pathological neural networks. High-frequency DBS appears to reproduce the clinical effect of ablative procedures. Moreover, at high frequencies DBS may abolish cortical epileptiform activity. A microthalamotomy effect has been postulated based on the observation that some patients obtain a reduction in seizure frec.

Abbreviations used in this paper: AC = alternating current; AED = antiepileptic drug; ANT = anterior nucleus of the thalamus; CMT = centromedian nucleus of the thalamus; CN = caudate nucleus; CNS = central nervous system; CS = cerebellar stimulation; DBS = deep brain stimulation; DC = direct current; EEG = electroencephalography; MTL = mesial temporal lobe; SNr = substantia nigra pars reticulata; STN = subthalamic nucleus.
quency prior to activation of the pulse generator. Other studies have failed to detect a lesioning effect in the immediate postoperative period.

Although the precise mechanism by which DBS reduces seizure activity is unclear, inhibition of neurons immediately adjacent to the area of applied current is probably involved. A reversible functional lesion may be generated in structures integral to initiating or sustaining epileptic activity. The applied current may inhibit neurons with a pathologically lowered threshold of activation. Alternatively, DBS may act on neuronal network projections to nearby or remote CNS structures originating from the area of stimulation. It is possible that targeting the seizure focus may also affect the epileptogenic network. This could take place through either activation of inhibitory projections or through the inhibition of excitatory projections.

Deep brain stimulation for movement disorders has met with widespread success and is increasingly being investigated for new indications such as chronic pain, obsessive-compulsive disorders, and even headache. Although DBS of targets such as the thalamus, cerebellum, and locus ceruleus has been performed in patients with psychiatric disorders or spasticity who also had seizures, technical limitations have prevented it from becoming an appropriate treatment option for patients with epilepsy alone. A resurgence of interest in DBS for epilepsy has arisen as a result of its successful use in movement disorders, as well as the technological improvements in the equipment. Multiple epilepsy centers throughout the world have performed trials over the years using DBS for epilepsy, targeting a variety of CNS structures. These trials have been based around 2 different strategies: 1) targeting of the CNS structures believed to have a “gating” role in the epileptogenic network, such as the STN or thalamus; and 2) targeting of the ictal onset zone with the theory that stimulation may lead to interference with seizure initiation. The latter strategy might ideally be used in patients with MTL epilepsy given the success in reducing seizures in patients after anterior temporal lobectomy. Mesial temporal lobe epilepsy is the most common form of medically refractory partial epilepsy. Patients with this condition have a long-term freedom from seizure rate of 60–75% after undergoing temporal lobectomy. In spite of undergoing satisfactory preoperative Wada testing, however, many of these patients will demonstrate a verbal memory deficit on postoperative neuropsychological evaluation. Moreover, patients with temporal lobe epilepsy in the absence of hippocampal sclerosis have an even greater risk of postoperative neuropsychological complications. Resection of a volumetrically normal left hippocampus in patients with temporal lobe epilepsy is associated with significant verbal memory dysfunction. Resection of a volumetrically normal right hippocampus is associated with a decline in postoperative visuospatial learning. Patients with medically refractory seizures of bilateral ictal onset are not suitable candidates for resection. Moreover, patients demonstrating widespread ictal onset are less likely to become seizure free after temporal lobectomy. After temporal lobectomy, the recurrence rate of seizures after a long period of seizure freedom is as high as 15%. Given that some of these patients must undergo implantation of electrodes prior to considering resection (due to inconsistencies in noninvasive evaluations), they may be ideal candidates for using MTL DBS with the same electrodes that were used for diagnostic purposes.

In summary, resective epilepsy surgery is not an ideal option for all patients with medically refractory epilepsy. It is an invasive, irreversible procedure associated with only modest success in patients with normal MR imaging results or a diffuse ictal onset zone, and carries a significant risk of postoperative neurological or neuropsychological decline. This combination of factors drives the search for alternative treatment options such as neuromodulation.

Animal Studies

Numerous animal models have been used to elucidate mechanisms of DBS action and its potential usefulness in the treatment of epilepsy. Animal epilepsy models have utilized pentylenetetrazol, kainic acid, bicuculline, picrotoxin, and kindling to induce seizures. Sinusoidal AC versus DC stimulation protocols, synaptic versus nonsynaptic inhibition, regional alterations in neurochemistry, and different anatomic targets are among the many variables investigated in these models. Finding effective targets for modulating epileptiform activity is arguably the most important, but most elusive variable in the quest to treat seizures with DBS. The authors of many animal studies have set out to identify new targets and help achieve a better understanding of the mechanism of action in accepted targets.

Cerebellar Stimulation

Cooke and Snider demonstrated that CS can modify or abruptly terminate seizure activity in various cerebral areas. Iwata and Snider observed that CS could terminate hippocampal seizures and prolong afterdischarges that had been induced by electrical stimulation. In 1962, Dow et al. showed that CS could alter EEG activity and reduce frontal lobe seizures in a model of chronic epilepsy in awake, unanesthetized rats. In the normal hippocampus, Fanardjian and Donhofer found that CS induced slow waves while activation-like patterns appeared simultaneously in the cerebrum. Mutani and colleagues demonstrated that CS temporarily reduced cobalt-induced spiking in the cerebral cortex of cats. Eight years later, Brown et al. reported on tissue reactions after 2 months of electrical stimulation in the cerebellum of monkeys undergoing CS. Light and electron microscopic analyses revealed that the mere presence of the electrode array on the surface led to attenuation of the molecular layer and loss of Purkinje cells in adjacent tissue. The authors also discovered that charge densities of up to 5 times the threshold needed for cerebellar efferent activation resulted in no additional cerebellar cortical damage beyond that produced by the mere presence of the electrode array. Brown and colleagues concluded that charge densities ≤ 7.4 μC/cm²/phase should be considered safe for stimulation of the human cerebellum, but that increasing the charge density beyond this would lead to damage of the conducting elements. Sufficient damage, it was theorized, could ultimately render the stimulation ineffective. In 1980, Laxer et al. reported inconsistent results when reviewing studies from 22 groups who used CS with a wide range of stimulation parameters. These authors were nonetheless able to draw 2 conclusions: 1) that stimulation
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of the vermis and superomedial surface is more effective than stimulation of the lateral hemisphere; and 2) that CS is most effective in the treatment of limbic system epilepsy and least effective in models of focal epilepsy of the sensorimotor cortex. In the same year, Ehler and associates reported on their efforts with unanesthetized, awake primates to determine the effects of CS on the activity of single cells within a chronic, alumina cream seizure focus in the motor cortex. They demonstrated that charge densities in the range of 3.2–4.0 μC/cm²/phase modified the excitability of neurons in their experimental seizure focus during both epileptic and nonepileptic activity. The authors concluded that the effects of CS, including changes in seizure threshold, are highly dependent on stimulus parameters.

**Hippocampal Stimulation**

Lian et al. tested the effects of DC stimulation and low-duty cycle AC stimulation (which more closely approximates that used clinically) in a hippocampal slice epilepsy model. They demonstrated that continuous sinusoidal, 50% duty-cycle sinusoidal, and 1.68% duty-cycle pulsed stimulation (120 μsec, 140 Hz) all suppressed low-Ca⁺ epileptiform activity. Continuous sinusoidal stimulation was also found to completely suppress picrotoxin-induced epileptiform activity in either uniform or localized fields. The AC stimulation resulted in an increase in the extracellular potassium concentration and neuronal depolarization blockade, and was not found to be slice orientation selective. In contrast, DC stimulation suppressed epileptiform activity only in the region surrounding the electrode and did so by membrane hyperpolarization. Moreover, suppression by DC stimulation was found to be orientation-selective although there was a lower threshold for suppression.

Jensen and Durand recently demonstrated that in vitro sinusoidal high-frequency stimulation suppresses axonal conduction when applied to the alvear axon field of rat hippocampus slices. Stimulation was found to suppress the alvear compound action potential as well as the antidromic evoked potential. Complete axonal suppression was observed as a 100% reduction in the amplitude of the evoked potential for the duration of the stimulus. Axonal suppression was dependent on stimulation amplitude and frequency but independent of duration. The stimulation frequency at which maximal suppression occurred was between 50 and 200 Hz, similar to that observed in most clinical DBS studies. The degree of suppression of axonal conduction correlated with a rise in extracellular potassium demonstrating that stimulation may block axonal activity through nonsynaptic mechanisms.

An in vivo study of continuous DBS of the hippocampus in epileptic rats demonstrated an increased threshold, decreased duration, and increased latency of afterdischarges evoked by kindling stimuli when compared with control animals. The treated group received 130-Hz DBS for 1 week and was compared to a control group which did not receive DBS. Deep brain stimulation had a direct effect on evoked afterdischarges; stimulation increased the afterdischarge threshold to 203 ± 13% in control animals (p < 0.01), increased the afterdischarge latency to 191 ± 19% (p < 0.05), and decreased afterdischarge duration to 71 ± 9% (p < 0.05) of controls. The effect was found to be persisting in that 1 week after discontinuing stimulation, there were similar, albeit smaller, differences in afterdischarge.

**Stimulation of the STN and SNr**

Deep brain stimulation of the SNr completely blocked amygdala-kindled seizures in 10 (43.5%) of the 23 rats studied by Shi and colleagues. Microwire electrodes were implanted into the SNr and amygdala of adult male rats. Seizures were produced by daily amygdala kindling, and DBS was delivered to the SNr bilaterally 1 second after kindling stopped. When the same amygdala kindling procedure was performed 24 hours later without DBS, the kindling failed to elicit any seizures in 6 of 10 rats. In 3 animals, only mild seizures appeared after amygdala kindling. Only 1 rat exhibited Stage 5 kindled seizures 24 hours after DBS was discontinued. In 9 rats the period of seizure suppression or reduction lasted for up to 4 days. The authors concluded that highly plastic neural networks may be involved in amygdala-kindled seizures and that DBS may exert long-lasting effects on these networks.

In contrast Usui and colleagues found no treatment effect when they tested SNr DBS in rats with kainic acid-induced seizures. They compared a group of rats with a unilateral SNr electrode to a a group with a unilateral STN electrode. A control group received no electrodes. Kainic acid was systemically administered to all 3 groups of rats to induce limbic seizures, and DBS of the STN or SNr was started immediately afterward; EEG changes and the magnitude of clinical seizures were then evaluated. The findings indicated that unilateral STN stimulation significantly reduced the duration of generalized seizures on EEG. Interestingly, the duration of focal seizures on EEG was prolonged by STN DBS, possibly a result of the suppression of secondary generalization. In addition, STN DBS reduced the severity of clinical seizures. The rats that received SNr DBS demonstrated no significant effect when compared to the controls. Usui and colleagues concluded that unilateral STN DBS suppresses secondary generalization of limbic seizures. The failure of SNr DBS to reduce secondary generalization was felt to imply that, although nigral influence on seizure propagation may be important, other antiepileptic mechanisms such as antidromic stimulation of the corticosubthalamic pathway may also be involved.

Vercueil et al. used high-frequency STN DBS to suppress seizures in a rat model of generalized seizures using Genetic Abscence Epilepsy Rats from Strasbourg. These animals exhibit spontaneous, nonconvulsive generalized seizures with concomitant bilateral synchronous spike-and-wave complexes on EEG and a behavioral pause. Bilateral high-frequency STN DBS (130 Hz, 60 μsec, intensity just below the dyskinesia threshold) suppressed the spontaneous seizures in these rats. Bilateral neurotoxic lesions of the STN only partially suppressed seizures, reducing epileptiform discharge duration by 60% compared to control rats with sham lesions. Unilateral high-frequency STN DBS with identical stimulation parameters was ineffective.

**Anterior Nucleus of the Thalamus Stimulation**

The hypothesis that the ANT participates in the propagation of some forms of seizures is supported by experimental animal studies. Low frequency (8 Hz) stimulation of the ANT has been found to be epileptogenic. Seizures
can be induced in guinea pigs by microinjection of kainic acid, bicuculline, or pentyleneetrazol into the ANT.\textsuperscript{37} Interruption of the mammillothalamic tracts by electrolytic lesions offers protection from the epileptogenic action of pentyleneetrazol.\textsuperscript{36} Hamani and coworkers\textsuperscript{28} discovered that bilateral high-frequency AN DBS delays the onset of status epilepticus after exposure to pilocarpine. In their study, adult Wistar rats underwent unilateral or bilateral ANT lesioning, or unilateral or bilateral AN DBS electrode placement. The control group received bilateral ANT electrodes but no stimulation. Seven days later, the animals were given pilocarpine, after which EEG recordings and ictal behavior were evaluated. In the control group, status epilepticus developed in 67\% of the animals with a latency period of 15.3 ± 8.8 minutes after pilocarpine administration. Neither unilateral ANT lesioning nor unilateral AN DBS significantly reduced the likelihood or latency of status epilepticus. Bilateral ANT DBS did not prevent status epilepticus (observed in 56\% of the animals), but did significantly prolong the latency to 48.4 ± 17.7 minutes (p = 0.02). Interestingly, no animals with bilateral ANT lesions developed status epilepticus after pilocarpine treatment.

Heterogeneous study populations and sometimes conflicting treatment results found in animal models unfortunately mimic the clinical arena in the treatment of intractable epilepsy with DBS. However, animal studies will undoubtedly continue to play a major role in the development of neuromodulation techniques used to treat seizures.

**Clinical Studies**

**Cerebellar Stimulation**

Cooper et al.,\textsuperscript{15} the first to report on CS for epilepsy, observed that 10 of the 15 patients in their trial experienced a reduction in seizure frequency of ≥ 50\% after a follow-up of up to 3 years. Anterior lobe stimulation appeared to be more effective than stimulation of the posterior lobe. Cerebellar biopsies, obtained in 5 patients at the time of lead placement, revealed a reduction in the molecular layer, decreased or absent Purkinje cells, and decreased stellate cells. One patient, whose epilepsy failed to respond to stimulation, died as a result of a seizure 17 months after electrode implantation. Davis and Emmonds\textsuperscript{38} subsequently discovered that 23 of 27 evaluable patients who underwent long-term CS (average follow-up 14.3 years) had an overall reduction in seizure frequency. Interestingly, 12 of the patients had a nonfunctioning stimulator at the time of the report, yet 5 were found to be seizure-free, and 7 had experienced a reduction in seizure frequency.

Wright and colleagues\textsuperscript{86} examined 12 patients with severe, intractable epilepsy who underwent CS under double-blind conditions for 6 months. The trial was divided into 3 phases, each lasting 2 months. Patients received 2 months of continuous stimulation (alternating from 1 cerebellar hemisphere to the other every minute), 2 months of contingent stimulation (during which both hemispheres were stimulated only while a button was pressed by the patient or a family member), and 2 months of no stimulation. The sequence of phases was randomly assigned and the patients, family members, and evaluators were blinded to each epoch. No reduction in seizure frequency occurred that could be attributed to stimulation. However, most patients reported a reduction in the duration and severity of seizures although this was not measured during the study.

Eleven patients considered that the trial had helped them and said that they wished to continue the “stimulation” at the conclusion of the trial.

In a more recent double-blind trial with 2 years of follow-up in 5 patients undergoing CS, Velasco et al.\textsuperscript{79} demonstrated improvement in seizure control. Beginning 1 month after implantation and for a period of 3 months, patients were assigned randomly to receive stimulation while 2 others had their stimulators switched off. After the fourth month, all patients received stimulation for the next 6 months. During the 3-month double-blind phase, the 2 patients with stimulation off demonstrated no difference in mean seizure rate compared to baseline. During the same phase, the 3 patients with stimulation switched on demonstrated a reduction in seizure rate to 33\% of baseline. At the end of the subsequent 6 months, all 5 patients had a mean seizure rate of 41\% of baseline (range 14–75\%). The improvement in generalized tonic-clonic seizures occurred earlier and to a greater degree than that for tonic seizures.

It is likely that CS causes activation of the Purkinje cells, exerting an inhibitory output on the deep cerebellar nuclei. Cerebellar stimulation probably reduces excitatory cerebellar output from these nuclei to the thalamus, leading to a reduction in output from excitatory thalamocortical projections and thus to inhibition of cortical activity.\textsuperscript{50} As with other targets, additional clinical trials are necessary to determine the value of CS in patients with medically refractory epilepsy.

**Hippocampal Stimulation**

Evidence strongly suggests that the hippocampus is involved in the initiation and propagation of temporal lobe seizures.\textsuperscript{60,71} Velasco and associates\textsuperscript{75} demonstrated that hippocampal stimulation using electrode grids or depth electrodes significantly reduced interictal spikes and abolished complex partial and secondarily generalized tonic-clonic seizures in 7 of 10 patients with intractable temporal lobe epilepsy. In a subsequent study the same authors observed that chronic hippocampal stimulation in 3 patients reduced seizure activity without affecting short-term memory.\textsuperscript{82} Vonck et al.\textsuperscript{87} conducted an open label trial involving 3 patients with complex partial seizures who underwent DBS of the amygdalohippocampal region. Two quadripolar DBS electrodes were implanted in each hemisphere through 2 occipital bur holes. This procedure was performed on the same day as placement of subdural grids and strips. The most anterior electrode on each side was placed in the amygdala. The second electrode was placed more posteriorly, in the anterior part of the hippocampus on each side, and patients were gradually tapered off AEDs until seizures were observed. During a trial phase, stimulation was applied to both the amygdalar and hippocampal electrodes. The frequency was set to 130 Hz and pulse width to 450 μsec. Pairs of adjacent contacts on the amygdalar and hippocampal electrodes were stimulated in a bipolar manner with the first and third contact on each electrode serving as cathodes. Individual pulses consisted of biphasic square waves. The criterion for placement of an implantable pulse generator for long-term stimulation was the
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finding of a reduction of interictal spikes in the stimulated area of > 50% during 7 consecutive days of the trial period. Seizure frequency under the long-term stimulation condition was then compared with the mean monthly seizure frequency recorded 6 months before electrode placement. At a mean follow-up of 5 months (range 3–6 months), all 3 patients had a > 50% reduction in seizure frequency. Antiepileptic drugs were tapered in 2 patients. No side effects of stimulation were noted by the patients. Vonck et al. subsequently published results in 7 additional patients who underwent amygdalohippocampal DBS and an average of 14 months of follow-up. Two patients had a seizure frequency reduction of 25%, 3 had a > 50% reduction, and in 1 patient complex partial seizures were abolished. One patient did not experience a significant change in seizure frequency, and none of the patients reported side effects.

Stimulation of the CMT

The CMT arises from the diencephalon and brain stem, projecting diffusely into the cerebral cortex as part of the ascending subcortical system. The CMT may play a role in the pathophysiology and propagation of seizures. Deep brain stimulation of the CMT may result in hyperpolarization and desynchronization of the ascending reticular and cortical neurons.

Fisher et al. implanted programmable stimulators into the bilateral CMT in 7 patients with intractable epilepsy (6 with tonic-clonic seizures and 1 with partial complex seizures) to test feasibility and safety. Stimulation was switched on or off in 3-month blocks, with a 3-month washout period in a double-blind, cross-over protocol. The stimulation was delivered as 90-μsec pulses, 1 minute every 5 minutes for 2 hours/day. They noted a mean reduction in tonic-clonic seizure frequency of 30% with respect to baseline when the stimulator was on compared to a decrease of 8% when the stimulator was off. Stimulation at low intensity produced no changes in EEG results, but high-intensity stimulation induced slow waves or 2–3 Hz spike waves with ipsilateral frontal maxima. When the stimulator trains were continued for 24 hours/day, 3 of the 6 patients with tonic-clonic seizures reported at least a 50% decrease in seizure frequency. No side effects were reported.

Andrade et al. discovered no short-term improvement in seizure frequency in 2 patients who underwent CMT DBS; one suffered from generalized tonic-clonic seizures and the other from partial epilepsy with secondary generalization. The patient with tonic-clonic epilepsy had a significant reduction in seizures during the 3 years of follow-up even though the stimulators were off for 2 of those years. Both patients had 1 year of worsened seizures during active stimulation. Adverse events during stimulation in these patients included intermittent nystagmus, auditory hallucinations, and anorexia. One of the patients subsequently underwent electrode implantation within the ANT.

A recent trial of CMT DBS in 13 patients with Lennox–Gastaut syndrome revealed an overall seizure reduction rate of 80% and significant gains in quality of life. Lennox–Gastaut syndrome is one of the most severe forms of childhood epilepsy characterized by drug-resistant generalized seizures in conjunction with mental deterioration. The overall prognosis is very poor with 90% of patients being mentally retarded and 80% experiencing continuing seizures into adulthood. The 13 patients who underwent implantation in this study tolerated the procedure well; however, in 2 patients the electrodes had to be explanted due to multiple repeated erosions through the skin. Three patients experienced no improvement in their ability scale scores due to persistent seizures, 2 were seizure-free at the 18-month follow-up, and 8 patients experienced progressive improvement (5 of the 8 became completely independent).

Although CMT DBS may result in a reduced frequency of generalized seizures, the outcomes in patients with complex partial seizures are mixed.

Stimulation of the STN

The abundant reported experience of DBS of the STN for treating patients with Parkinson’s disease makes this a familiar and attractive target. The SNr appears to be involved in propagation of seizures through projections that transmit γ-aminobutyric acid to the superior colliculus. Inhibition of the SNr neurons suppresses partial and generalized epileptic seizures in a rat model of epilepsy. It is recognized that STN outputs produce an excitatory influence over the SNr system, and that electrical or pharmacological inhibition of the STN in rats can result in seizure suppression.

Benabid and colleagues reported that high-frequency bilateral STN DBS in a child with cortical dysplasia and inoperable epilepsy resulted in an 83% improvement in seizure frequency after 30 months, a reduction in seizure severity, and a recovery of motor function. In the same report, the authors noted a 50% reduction in seizures in 1 patient with severe myoclonic epilepsy undergoing bilateral STN DBS.

Loddenkemper et al. reported on 5 patients undergoing STN DBS for pharmacologically intractable seizures. The patients received constant stimulation at 100 Hz, with a stimulus duration of 60 μsec. In 2 of these patients, an 80% reduction in seizures was noted after 10 months and a 60% reduction after 16 months. The authors hypothesized that the dorsal midbrain anticonvulsant zone in the superior colliculus is under the inhibitory control of efferent projections from the SNr. In this model, inhibition of the STN is believed to reduce the inhibitory effect of the SNr on the dorsal midbrain anticonvulsant zone, thereby raising the seizure threshold.

In their open-label study of STN DBS, Chabardes et al. implanted electrodes in 5 patients with medically intractable seizures who were considered unsuitable for resection, and a 67–80% reduction in seizure frequency was noted in 3 of them. A fourth patient with severe myoclonic epilepsy (Dravet syndrome) had a less impressive reduction. The fifth patient, who showed no improvement with treatment, suffered from an autosomal dominant form of frontal lobe epilepsy.

More recently, Handforth and colleagues reported their results with bilateral STN DBS in 2 patients with refractory partial-onset seizures. In 1 patient, seizure frequency was reduced by one-third, and the patient’s quality of life was improved as a result of milder, less harmful seizures. The other patient continued to have seizure-related injuries despite a 50% reduction in seizure frequency. To better
understand the potential of STN DBS as a treatment for medically refractory epilepsy; more trials will be necessary.

Caudate Nucleus Stimulation

The caudate loop is a functional unit made up of the neocortex, thalamus, and head of the CN. Chkhenkeli et al. performed test stimulation of the head of the CN in 57 patients, 17 of whom went on to receive neurostimulator implantation for therapeutic purposes. One of 4 different stimulation protocols was used, depending on the duration and frequency of background epileptic activity achieved during test stimulation. In the first protocol, a continuous regimen of 12–14 hours/day of stimulation was used. In the second, patients received intermittent stimulation for 12–14 hours/day with a cycle of 10 minutes on and 15–20 minutes off. The third treatment regimen consisted of continuous stimulation for 20–30 minutes, 3 or 4 times per day (5 minutes on and 5 minutes off). The intensity of stimulation was periodically increased over the course of treatment. A fourth protocol allowed the patient to operate a closed-loop system, during which the patient could activate the stimulator on sensing an aura. The authors discovered that short duration, high-frequency stimulation (30–100 Hz for 2–5 seconds) of the dorsal and ventral head of the CN produced enhancement of epileptiform spikes and/or sharp wave activity. By contrast, low-frequency stimulation (4–8 Hz) of a similar duration reduced the frequency of sharp transient spikes in the interictal epileptic activity and truncated epileptic discharges from the temporal neocortex. Overall, 14 of 17 patients experienced a reduction in seizure frequency. The authors also noted that unilateral low-frequency stimulation had a suppressive effect not only on the ipsilateral interictal activity, but also on contralateral focal discharges. They postulated that activation of the head of the CN results in hyperpolarization of the cortical neurons, and that stimulation-induced inhibition can theoretically suppress seizure activity.

Stimulation of the ANT

Low-frequency stimulation (8 Hz) of the ANT has been found to be epileptogenic. Seizures can be induced in guinea pigs by microinjection into the ANT of the excitatory agents kainic acid, bicuculline, or pentyleneetrazol. Interrupting the mammillothalamic tracts by electrolytic lesions offers protection from the epileptogenic action of pentylenetetrazol. The placement of DBS electrodes bilaterally into the ANT delays the onset of status epilepticus after exposure to pilocarpine. Given the absence of an anticonvulsant effect noted in numerous studies, as well as the proconvulsant effects noted in others, the efficacy of long-term ANT DBS for epilepsy in animal studies remains incompletely defined. To date, only small pilot studies have been performed to evaluate the use of ANT DBS as a treatment for medically refractory seizures. Although there has been significant variability in outcome from one study to another, bilateral high-frequency ANT DBS appears to be a safe and effective treatment for some patients with medically refractory epilepsy.

Upton and colleagues treated 5 men and 1 woman (mean age 23.7 years) with debilitating, medically refractory seizures by pulsed electrical stimulation of the ANT. In 4 patients, a statistically significant reduction in seizure frequency was obtained. In 2, changes in regional cerebral glucose metabolism, serum levels of AEDs, and serum cortisol levels were observed with stimulation both on and off. The authors concluded that stimulation of the ANT produces not only clinical and EEG changes, but also changes in cerebral metabolic, endocrine, and pharmacokinetic responses.

Osorio and colleagues recently reported on the safety and efficacy of high-frequency ANT stimulation in patients with inoperable MTL epilepsy. Four patients underwent bilateral implantation of DBS leads into the ANT, followed 6 weeks later by generator implantation. The mean stimulation parameters were 175 Hz, 4.1 V, and a pulse width of 90 μsec. The stimulation was intermittent with 1 minute on and 5 minutes off. The efficacy of stimulation was evaluated by comparing seizure frequency over a 36-month treatment period to a 6-month baseline period recorded prior to implantation. The authors noted a mean reduction in seizure frequency of 75.6% (range 53–92%). Quality of life indices improved in all 4 patients, and no serious adverse events were reported. Interestingly, evoked responses (recorded from depth electrodes placed in the amygdalohippocampal region) from each patient during ANT stimulation demonstrated significant variability between individuals, which was interpreted as implying a nonuniform lead placement. Moreover, the evoked responses changed depending on the stimulation parameters. The authors concluded that high-frequency, intermittent thalamic stimulation is safe and efficacious in patients with inoperable MTL epilepsy. They interpreted the variability in evoked responses to indicate that selective stimulation of a single CNS structure may not be required to demonstrate efficacy in reducing seizure frequency.

Lee et al. reported on 6 cases of medically refractory, surgically inoperable epilepsy in patients implanted with DBS electrodes (in the ANT and in the STN). Seizure frequency and severity were observed and compared to baseline prior to surgery. The stimulators were turned on 1 week after insertion of the electrodes. The patients with implantation in the ANT experienced a 75.4% reduction in seizure frequency, whereas those with STN electrodes had their seizure frequency reduced by 49.1%. An infection developed in 1 patient.

Long-term follow-up was reported by Lim et al. in 4 patients who underwent bilateral DBS implantation within the ANT. All patients underwent microelectrode recording, postoperative MR imaging, and activation of the stimulator 2–4 weeks after implantation. The initial stimulation parameters were 90–110 Hz, 4–5 V, and 60–90 μsec. For each patient, seizure frequency at baseline and after implantation was analyzed. A two-tailed, single-value t-test was performed to assess for differences in seizure frequency between the postimplantation stimulation off (sham) interval, and the on interval. The average seizure frequency during a 6-month period of cycled stimulation was compared to a continuous stimulation interval of similar duration. A one-way analysis of variance test was performed to evaluate for the influence of AED adjustment on seizure frequency. Intelligence quotient tests and auditory P300 responses were performed before and after surgery to evaluate for any cognitive decline. An average reduction in seizure frequency of 67% (range 44–94%), was noted during the shan interval. Once the stimulators were turned on,
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a 49% (range 35–76%) reduction in seizure frequency was noted over the subsequent follow-up period (mean 43.8 months, range 33–48). In 1 patient the stimulator was inadvertently turned off during months 7–12, during which period the seizure frequency increased compared to baseline. No significant difference in seizure frequency was noted between the cycling and continuous stimulation intervals. One patient was seizure-free on AEDs for 15 months after implantation. No permanent neurological complications were observed, although 1 patient had a small frontal hemorrhage, and an infection developed in another patient, requiring removal of the entire system. Postoperative IQ index and auditory P300 responses were unchanged compared with baseline values. Although a reduction in seizure frequency was noted during this study, the authors could not determine whether the lesioning effect, subsequent stimulation, or changes in AEDs had the greatest impact.

Hodaie et al.33 implanted bilateral DBS electrodes in the ANT of 5 patients with medically refractory epilepsy who were not eligible for resection. Microelectrode recordings were performed and postoperative CT or MR images were obtained in all patients to confirm proper electrode placement; the stimulators were then turned on 4 weeks after implantation. The stimulation parameters were 100 Hz, 10 V, and 90-μsec pulse width, cycling 1 minute on and 5 minutes off, alternating left and right sides. Antiepileptic medications were unchanged for the duration of the study. In each patient, pre- and postoperative seizure rates were evaluated using the one-way analysis of variance (F test). The average follow-up time was 14.9 months (range 10.6–20.7 months). After implantation, the authors noted a statistically significant decrease in seizure frequency compared to baseline (p < 0.05). The seizure reduction rate was 24–89% (mean 53.8%), and 2 patients had a > 75% reduction in seizure frequency. Hodaie and associates noted that merely inserting the electrodes resulted in reduced seizure frequency, and that turning the stimulator on at 4 weeks yielded no additional reduction. After an interval of continuous stimulation ranging from 7 to 17 months, each of the patients had their stimulators turned off in a blinded fashion for 2 months. Seizure rates were then compared between the stimulation on and off intervals, and no significant difference in the rate of seizure reduction was observed between them. The only adverse surgical event was erosion of the skin over the DBS site, requiring revision surgery in 1 patient.

Kerrigan et al.38 conducted an open-label pilot study in 5 patients to investigate the safety and tolerability of bilateral ANT stimulation and to investigate the range of appropriate stimulation parameters. Patients enrolled in the study had medically intractable partial seizures and were not candidates for resection. Four of the 5 patients also suffered from secondarily generalized seizures. Microelectrode recording was used in 3 of the 5 patients. During implantation on each side, the patients received unilateral stimulation with simultaneous recording of scalp EEG to determine the threshold, if obtainable, of a driving response. The stimulation parameters during implantation were intensities of 1–10 V, pulse widths of 90–330 μsec, and a frequency of 5–10 Hz. After completing implantation, long-term ANT stimulation was then performed intermittently, with the stimulator on each side programmed to produce 1 minute of stimulation every 10 minutes. Stimulation on each side was offset by 5 minutes. Stimulation parameters were: frequency of 100 Hz, pulse width of 90 μsec, and intensity of 1–10 V. The voltage was incrementally increased over a period of 12–30 weeks, depending on the clinical response of each patient. Seizure counts were monitored through the use of daily diaries and were compared to baseline seizure frequency. Antiepileptic drug regimens were unchanged during the first 3 months of stimulation, but were adjusted thereafter. No hemorrhages were discovered on postoperative imaging and there were no wound infections. All 5 patients demonstrated EEG-driving responses during low-frequency stimulation with greatest amplitude ipsilateral to the side of stimulation. The baseline average monthly seizure frequency across all 5 patients was 46.8 ± 26.4 (mean ± standard deviation). During the 12-month treatment period of high-frequency stimulation, the average monthly seizure frequency for the group dropped to 25.0 ± 11.5 (mean ± standard deviation), although this was not a statistically significant difference from the baseline frequency. Only 1 patient experienced a statistically significant (p < 0.05) reduction in overall seizure frequency, and in 4 patients a reduction in the incidence of injurious seizures to < 50% of baseline was demonstrated.

Andrade et al.3 reported on the long-term follow-up in 6 patients who underwent bilateral ANT DBS for epilepsy. All patients included in the study had to have frequent and disabling seizures not responsive to multiple AEDs, have no lateralizing structural abnormality visible on brain MR images, and be willing to keep seizure diaries for 3 months before and 1 year after implantation. Three patients had generalized epilepsy with tonic-clonic seizures, while the other 3 had multifocal/partial epilepsy with secondarily generalized seizures. Programming was initiated 1 month after insertion of electrodes. All patients underwent postoperative MR or CT imaging to verify electrode positioning, and their AED regimens were not changed during the 2 years of follow-up study. Stimulation parameters were: frequency of 100–185 Hz, intensity of 1-10 V, and pulse duration of 90–120 μsec. The first 5 patients implanted underwent a 2-month, single-blind period of sham stimulation, during which the generator was off. Implantation of the DBS electrodes resulted in a statistically significant reduction in seizure frequency in all 6 patients. Five had a reduction in seizure frequency of 50% or greater, although 2 of these reported no benefit until Years 5 and 6, and only after changes in their AED regimens. Changes made to stimulation parameters could not be correlated with success in seizure control. Moreover, during the single-blind, 2-month period when the stimulation was turned off, there was no difference in seizure rates. In addition, no hemorrhages or infections were reported. The only adverse event was a 4-day period of lethargy in 1 of the patients; otherwise, even at maximum voltage, the patients could not tell whether their stimulators were on or off. Table 1 summarizes the stimulation parameters used and outcomes obtained in clinical studies of DBS to treat medically refractory epilepsy.

Conclusions

In spite of optimal medical management, many patients with epilepsy show no response to medical treatment and
suffer from debilitating seizures. Many patients with medically refractory epilepsy are not candidates for surgery because of the inability to localize a resectable focus. Some of these patients may benefit from DBS. A variety of targets may be suitable for implantation, and no current studies exist that definitively favor one target over another. Additional studies are needed to identify the appropriate patient population for DBS, the optimal target, and the best stimulation parameters. It may be that a complex pathological entity as heterogeneous as epilepsy cannot be embraced as a treatment option for epilepsy. The wide spectrum of results produced by DBS for epilepsy in animal and clinical experiences in the literature is probably due to the diversity of paradigms and parameters used.

Advanced diagnostics, including magnetoencephalography and modern functional imaging, will probably play an increasing role in determining appropriate treatment targets. Although it has already met with some success in the clinical arena, the successful future of DBS for the treatment of refractory epilepsy is contingent on the continued collaboration of the clinician and scientist. Our technical capabilities have grown at a rate that may well have surpassed our understanding of the complex neurobiology that we aim to modulate. A greater knowledge of which local electrical and neurochemical alterations have led to success in current stimulation models will help ensure reproducibility in future. Understanding these relationships may enable future technologies, perhaps even nanotechnologies, to flourish in the developing field of therapeutic neuro-modulation.

### Disclaimer

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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Address correspondence to: Thomas L. Ellis, M.D., Department of Neurosurgery, Wake Forest University School of Medicine, Winston-Salem, North Carolina 27157. email: tlellis@wfubmc.edu.