Disrupting abnormal electrical activity with deep brain stimulation: is epilepsy the next frontier?

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Given the tremendous success of deep brain stimulation (DBS) for the treatment of movement and neuropsychiatric disorders, clinicians have begun to open up to the possible use of electrical stimulation for the treatment of patients with uncontrolled seizures. This process has resulted in the discovery of a wide array of DBS targets, including the cerebellum, hypothalamus, hippocampus, basal ganglia, and various thalamic nuclei. Despite the ambiguity of the mechanism of action and the unknowns surrounding potentially ideal stimulation settings, several recent trials have empirically demonstrated reasonable efficacy in selected cases of medication-refractory seizures. These exciting results have fueled a number of studies aimed at firmly establishing DBS as an effective treatment for selected cases of intractable epilepsy, and many companies are aiming at Food and Drug Administration approval. We endeavor to review the studies in the context of the various DBS targets and their relevant circuitry for epilepsy. Based on the unfolding research, DBS has the potential to play an important role in treating refractory epilepsy. The challenge, as in movement disorders, is to assemble interdisciplinary teams to screen, implant, and follow patients, and to clarify patient selection. The future will undoubtedly be filled with optimization of targets and stimulation parameters and the development of best practices. With tailored therapeutic approaches, epilepsy patients have the potential to improve with DBS. (DOI: 10.3171/2010.4.FOCUS10104)

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Epilepsy affects approximately 50 million people worldwide.85 Despite active AED development, up to 20% of patients suffer from poor seizure control even with optimal medical therapy.64 A subset of these patients will be candidates for ATL, which in reported series has resulted in 80%–90% seizure freedom.74 For the remaining patients, alternative therapies such as VNS,20 lesionectomy, and multiple subpial transections have proven limited in efficacy. Given the tremendous success of DBS for the treatment of movement and neuropsychiatric disorders,53,62 clinicians have begun to explore the potential of electrical stimulation for the treatment of a select group of patients with medication-refractory epilepsy.

These investigations are especially exciting as they have the potential to further elucidate understanding of brain circuitry as well as propagation and abortion of seizures.40 Empirical trials have resulted in the discovery of unlikely DBS targets, including the cerebellum, hypothalamus, hippocampus, basal ganglia, and various thalamic nuclei.28 Additionally, DBS for epilepsy has reinvigorated interest in the possible positive neuronal changes that may occur secondary to chronic stimulation, and that may have benefits even when stimulation has ceased (for example, when batteries of devices burn out or closed-loop devices are employed).34 This idea of neuronal-level changes is based in part on the phenomenon of secondary epileptogenesis in patients with long-term, poorly controlled seizures. Deep brain stimulation may be used to address the challenge of repeated ictal insults initiated from a single site eventually inducing remote and independent ictal activity derived from other structures.5,34,40,47,61

Despite recent FDA hearings for approval of DBS for epilepsy, DBS remains investigational. The mechanisms by which DBS addresses seizures—or even movement

Abbreviations used in this paper: AED = antiepileptic drug; AN = anterior nucleus; ATL = anterior temporal lobectomy; CMN = centromedian nucleus; CN = caudate nucleus; DBS = deep brain stimulation; MB = mamillary body; MMT = mamillothalamic tract; MTL = mesial temporal lobe; SNr = substantia nigra pars reticulata; STN = subthalamic nucleus; VNS = vagal nerve stimulation.
disorders—are not completely understood. Some theorize that electrical stimulation results in the release of inhibitory neurotransmitters.22 Others posit that stimulation inactivates neurons via depolarization blockade,59 although most movement disorders experts agree this is probably not the mechanism of action. The benefits of DBS are likely the result of synaptic-level, neurochemical and neurophysiological changes.26,27 Recently it has been discovered that DBS may actually inhibit cells close to an electrical field and excite those farther from it.31,44,48 Stimulation of deep nuclei with broad-ranging connections to cortical structures makes DBS treatment especially attractive for epilepsy patients with multiple foci of seizure onset.

The timing and targets of electrical stimulation delivery are also an area of active research. Chronic stimulation with an "open-loop" system has been challenged by stimulation only in response to a cue (seizure) referred to as "closed-loop" treatment. Multiple targets have been evaluated for DBS in epilepsy with variable results. One of the reasons that studies have reported variable results with the same DBS target may be that certain seizure types will respond differently to stimulation of a particular target. Despite all the uncertainty, several trials have empirically demonstrated the efficacy of DBS for seizures, even in patients in whom other therapies have failed. These exciting results have fueled a number of studies designed to firmly establish DBS as an effective treatment for intractable epilepsy. In the following sections, these studies will be reviewed in the context of the various DBS targets for epilepsy and the relevant circuitry involved.

Potential DBS Targets

Most targets for electrical stimulation are deep nuclei with broad connections. These connections allow stimulation of the deep nucleus to modulate areas of cortex that produce seizure activity.31,32 In contrast, a handful of trials have tested stimulating the seizure foci directly, such as the hippocampal and hypothalamic hamartoma trials. Both indirect and direct targets will be reviewed here.

Hypothalamus

The posterior hypothalamus, specifically the mamillothalamic tract (MTT) (and possibly its association with the circuit of Papez3). In guinea pigs, bilateral lesions of the MB and MTT resulted in a significant decrease in the presence and lethality of seizures induced by the drug pentylenetetrazol.48,49 These studies led to a pilot study in 3 patients who had depth electrodes implanted bilaterally in the MB and MTT. One of these patients was found to have ictal activity without scalp electroencephalographic changes, giving credence to the notion that subcortical structures can be responsible for ictal activity.75 Subsequently, MB/MTT DBS was evaluated in patients with seizures secondary to hypothalamic hamartomas.36 Given the risks associated with tumor resection, 2 patients underwent placement of MB/MTT DBS ipsilateral to the tumor. Both had significant reductions in seizure frequency, with 1 patient reporting seizure-freedom at the time of publication.36 Although these results are compelling, hypothalamic stimulation will require further study to fully understand its utility for epilepsy, and selection criteria and approaches will need to be defined.

Hippocampus

The hippocampus has been a rational target for epilepsy treatment given the prevalence of mesial temporal lobe (MTL) epilepsy. Select patients with MTL epilepsy who do not respond to medical therapy are considered candidates for amygdalohippocampectomy. Multiple groups have reported excellent results (significant seizure reduction in 80%–90% of patients)54 with this procedure. On the other hand, those with bilateral onset of seizures or with a unilateral focus that spreads to the dominant hemisphere have not traditionally been surgical candidates due to the potential risk to language and memory areas associated with bilateral resections or large dominant lobe resections.12,67 With these patients in mind, Velasco et al.76 studied hippocampal stimulation in 2 groups of patients. In the first group, 2 patients had placement of bilateral deep electrodes and 8 patients had unilateral surface electrode grids placed. These patients underwent hippocampal stimulation at 130 Hz for 2–3 weeks and subsequently underwent an ATL. The second group was made up of 3 patients who underwent placement of unilateral or bilateral electrodes with a pulse generator for stimulation for at least 3–4 months. The investigators found that hippocampal stimulation abolished clinical seizures and significantly decreased the number of interictal spikes in both groups studied. They did not observe any histopathological changes in the patients who underwent subsequent resection. Additionally, they found that stimulation resulted in SPECT hypoperfusion of the hippocampal region, leading to the hypothesis that stimulation resulted in neuronal inhibition.77

In 2007, after reporting good results in a pilot study involving 3 patients,82 Boon et al.10 reported on 10 patients with either unilateral or bilateral seizure onset of MTL epilepsy treated with DBS. The DBS leads were placed bilaterally with electrodes in the amygdala and hippocampus. Seven of the patients (70%) had at least a 50% reduction in seizures (one patient was seizure free).90 Two patients had seizure frequency reduction of 30%–49% and one patient was a nonresponder. Only one patient experienced an adverse event; asymptomatic intracerebral hemorrhage was discovered on imaging to be tracking along the DBS lead trajectory. These patients were compared with 2 patients who underwent amygdalohippocampectomy who were seizure free for more than 1 year.

Patient outcomes, however, were not as robust in the only double-blind trial.89 In this study, 4 patients with MTL epilepsy underwent placement of unilateral DBS electrodes in the hippocampus. Patients had continuous stimulation at 190 Hz and were randomized to 3 treatment pairs each with an “on” and an “off” period under double-blind conditions. During the “on” period, patients experienced a median reduction in seizure frequency of 15%, but this failed to reach statistical significance. The patients did have continuous adjustment of AEDs during the study, and given the seizure-frequency improvement during the “off” periods, the patients may have benefited from lead
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placement alone (lesional effect). A subsequent trial of bilateral hippocampal stimulation (in 2 patients) revealed no decrease in seizure load after implantation and prior to initiation of stimulation, making lesioning a less likely explanation in this cohort. Importantly, none of the patients had changes in memory, cognition, or emotion.

The hippocampus continues to be evaluated as a direct target for treatment of MTL epilepsy. With subdural or DBS electrodes, the hippocampus is a viable target structure, especially for patients who are otherwise not surgical candidates for epilepsy treatment such as those with bilateral temporal lobe foci or large dominant lobe foci.

Cerebellum

After the discovery of the importance of cerebellar Purkinje cells in the generation of widespread inhibitory discharges, Cooper et al. described cerebellar stimulation as a potential treatment for epilepsy. Building on older animal studies showing that the inhibitory influence of the cerebellum may be important in terminating seizures, Cooper et al. published the first description of noncortical stimulation for seizures, describing 7 patients who underwent placement of cerebellar electrodes for intractable epilepsy. Six patients had significant clinical improvement, and the authors reported only one complication (posterior fossa hematoma requiring evacuation). This same group subsequently described cerebellar stimulation in 15 epilepsy patients (with psychomotor, generalized tonic-clonic, or myoclonic seizures) in 1976. Ten of the 15 patients had clinical benefit (some with complete cessation of seizures), although both studies used suboptimal outcome measures. One patient who did not have seizure control died at home from a nocturnal seizure. The details of stimulation were variable, but based on their experience, the authors recommended anterior cerebellum stimulation with a frequency of 10 Hz. Other retrospective studies have also demonstrated improvement of epilepsy with high-frequency stimulation. Stimulation of the cerebellum is hypothesized to have its effect by action on the output to the ventrolateral nucleus of the thalamus and subsequently the exertion of decreased excitatory output to the cortex.

These promising results were tempered by subsequent reports that failed to reveal similar efficacy. In a follow-up analysis of 5 cases involving patients who underwent cerebellar stimulation using 10 Hz for 10-minute periods, no difference in seizure frequency was found. Patients continued their AED treatment during the study and were monitored in the hospital for 4- to 6-week periods over 15–21 months. Similarly, another double-blind analysis of results in 12 epilepsy patients used 10 Hz of cerebellar continuous stimulation for 2 months, then 2 months of contingent stimulation followed by 2 months of no stimulation. Eight of the patients experienced some sort of morbidity (infection or CSF leak), and no difference in seizure frequency was observed. Despite these findings, 11 patients felt the trial had helped them, emphasizing the problems with using patient reports as an outcome variable instead of a validated, sensitive instrument.

In the largest uncontrolled study, 27 of 32 patients, described as having spastic or epileptic seizures, were treated with cerebellar stimulation and were evaluated for long-term follow-up. Overall, 85% (23 of 27) had some benefit from stimulation (12 had benefit despite nonfunctioning stimulators due to battery life termination, suggesting a potential lesional or long-term effect). In a small double-blind pilot study, significant reductions in seizure frequency were described in 3 patients with active cerebellar stimulators compared with 2 patients with cerebellar stimulators that were placed in the off position. Given the mixed results from a few existing trials and the inclusion of patients with multiple types of epilepsy in these trials, a well-powered randomized controlled trial with careful patient selection will be necessary to establish a consensus about the utility of cerebellar stimulation for seizure control.

Subthalamic Nucleus

The STN is one of the most common Parkinson disease DBS targets. This nucleus, which is located atop the substantia nigra pars reticulata (SNr), lateral to the red nucleus and just below the zona incerta, plays a major role in the direct and indirect motor pathways implicated in the pathogenesis of Parkinson disease. The STN possesses sensorimotor, limbic and associative areas and connections. While the sensorimotor areas are located primarily in the dorsolateral region, the limbic region is more medial and the associative area more dorsomedial. These areas may provide reasonable individual targets for various symptoms and diseases.

The first evidence that the STN plays a role in epilepsy came from animal studies. Injection of an N-methyl-D-aspartic acid (NMDA) antagonist into the SNr suppressed seizures in a model of genetic absence epilepsy in rats. Subsequently, based on anatomical and clinical evidence of the intimate relationship between the SNr and STN, it was shown that high-frequency stimulation of the STN was able to suppress seizures in the rat model. In the earliest report of using STN DBS for human epilepsy, Benabid et al. described 3 cases of bilateral STN DBS in which there was a decrease in seizure frequency of 50%–80%. One patient had an infection, and removal of the infected electrode resulted in an increased seizure frequency. Interestingly, the frequency did not revert to preimplantation levels.

Another study by Lee et al. compared 3 patients who were implanted with STN DBS to 3 patients receiving implants in the anterior nucleus (AN) of the thalamus. The AN stimulation group had greater suppression of seizure activity (75% compared with 50%). In the STN DBS group, there was a substantial increase in regional cerebral blood flow in the frontal zones presumed to be related to epileptogenesis, and the authors suggested this as a mechanism of seizure reduction. These findings suggest that select patients with frontal foci and spread of epileptic activity may be best treated with STN DBS, though more controlled studies must be done.

Centromedian Thalamic Nucleus

The CMN is an important structure in the reticulo-cortical system, and it plays a vital role in wakefulness and consciousness. It also has potentially important roles as a motor and limbic relay station. Early animal
studies implicated the CMN in cortical excitability in generalized seizures. Anatomical as well as neurophysiological data have established the CMN as a "gate-keeper" in rhythm-generating activities, and therefore as a potential target for the treatment of seizures. Empirically, chronic electrical stimulation of the CMN was first explored by Velasco and colleagues in 1987. Five patients with refractory, primary generalized, or multifocal seizures underwent placement of electrodes in the CMN bilaterally. They were treated with pulses in trains of 1 minute every 5 minutes alternating right and left for 2 hours per day. After 3 months of treatment, the patients reported an 80%–100% decrease in generalized tonic-clonic seizures and a 60%–100% decrease in partial complex seizures. Interestingly, in this report the authors also mention 2 patients who were treated with red nuclei stimulation with no clinical benefit. Building on these impressive results, the same group later published the largest series of CMN stimulation, reporting efficacy for generalized tonic-clonic seizures and atypical absences, but not for partial seizures. These data were not quantified or evaluated statistically, and the outcome measures and methodology have come under scrutiny.

The only controlled trial (double-blind, crossover) of CMN stimulation was published by Fisher et al. Seven patients had surgery for placement of bilateral CMN stimulators and underwent 3-month periods of "on" or "off" stimulation. Stimulation was delivered as 90-μsec pulses at a rate of 65 Hz, 1 minute of each 5 minutes for 2 hours/day. Generalized tonic-clonic seizures were reduced by 30% when the stimulators were on as compared with 8% when the stimulators were off. Nevertheless, given the limited power of the study, this difference did not reach statistical significance. The authors did show, however, that seizure reduction was more marked when stimulators were on all day versus only 2 hours per day.

Electrical stimulation of the CMN has produced some exciting results in the treatment of seizures, especially those of a generalized tonic-clonic type. Nonetheless, anecdotal experience has shown variable results with some adverse events reported (nystagmus, hallucinations, and amnestic impairment), and the future of thalamic CMN stimulation for epilepsy remains unclear.

**Anterior Nucleus of the Thalamus**

Similar to the CMN, the AN is a viable target for DBS due to its gate-keeping activity in seizure propagation. It has wide-ranging projections to multiple structures, including the cingulate cortex, amygdala, hippocampus, orbitofrontal cortex, and CN, and receives input from the mammillary bodies. Uniquely, the AN of the thalamus is not under the control of the reticular thalamic nuclei. Stimulation of the AN has had mixed results in animal models of epilepsy, with some investigators reporting benefit and others reporting increased seizure frequency. Targeting of the AN is more practical compared with targeting of other subcortical sites owing to the fact that the AN is large and well defined for surgical approaches by stereotaxy.

Preliminary data suggest that AN DBS has more potential than some of the other targets for the treatment of epilepsy. Upton et al. first reported a decrease in seizure frequency in 4 of 6 patients treated with chronic bilateral AN stimulation at 60–70 Hz. Subsequently, a study of 3 patients who were treated with bilateral AN stimulation found a 75.4% decrease in seizure frequency. Lozano's group in Toronto published another study of 5 patients with a wide range of epilepsy types (generalized tonic-clonic, atonic, complex partial, and partial motor), and demonstrated a mean seizure frequency reduction of 53.8% (p < 0.05 compared with preoperative seizure frequency) with bilateral intermittent AN stimulation. The improvement in seizure frequency was seen after implantation and before stimulation—meaning no additional benefit was achieved with stimulation, suggesting a strong possibility of a lesional effect. Similar seizure reduction results were reported in other small studies with minor or acceptable complication rates.

These results finally culminated in a multicenter, randomized trial (SANTE) of 110 patients to attempt to demonstrate the effectiveness of bilateral stimulation of the AN. This trial was double-blinded, and the patients in both study arms received electrode implantation. In those in the control arm the electrode was not activated for 3 months while in those in the experimental arm it was activated immediately. During stimulation, patients received 5-V, 90-μsec pulses for 1 minute alternating with no stimulation for 5 minutes. The patients in the experimental arm had a 29% greater reduction in seizures than the control group (p = 0.002). The median seizure frequency decrease was 14.5% in the control group and 40.5% in the experimental group. No significant complications resulted from the procedure. Furthermore, the benefits from stimulation lasted for the duration of the study with a 56% median percentage reduction in seizure frequency at 2 years. Six patients were seizure free for at least 6 months at 2-year follow-up. However, the authors noted that patients with seizure foci in the frontal, parietal, or occipital lobes did not have any significant improvement with AN stimulation. Only the patients with seizures of temporal lobe origin had a significant decrease in seizure frequency with AN stimulation. Nonetheless, these results make AN the most well-established target for DBS in the treatment of epilepsy to date, and these data will help the field to establish patient selection criteria (for example, seizures of hippocampal origin may be more amenable to neuromodulation).

**Caudate Nucleus**

Although the CN is not as well studied as the thalamic nuclei, it may be the only deep target site where low-frequency electrical stimulation is efficacious in the treatment of epilepsy. However, there remains a paucity of information from which to draw this conclusion. Chkhenkeli et al. achieved improvement in bilateral epileptic discharges with low-frequency (4–8 Hz) unilateral CN stimulation in 57 patients. In contrast, high-frequency stimulation resulted in increased epileptic activity in the ipsilateral hemisphere. This phenomenon has been hypothesized to be a result of low-frequency stimulation causing cortical hyperpolarization and resultant clinical benefit. Nevertheless, these studies did not quantify the...
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results or include statistical analysis. The study populations included patients who had partial-onset seizures as well as temporal lobe foci. Furthermore, a significant proportion had previously undergone ablations or lobectomies, and the methodology for seizure evaluation was not standardized. Further trials will need to be conducted to evaluate the usefulness of the CN as a target site for epilepsy treatment.

Closed-Loop Systems

Most of the studies evaluating electrical stimulation for the treatment of epilepsy involve open-loop systems due to the technical complexity of delivering an impulse in response to seizure activity. Yet, in vitro and in vivo animal studies demonstrate increased efficacy of suppressing spikes when stimulation is instituted in response to seizure activity, in contrast to random electrical stimulation. The first attempts at seizure-responsive electrical stimulation involved large nonimplantable bedside systems. One of these systems was evaluated in 8 patients, 4 with responsive stimulation directly in the epileptogenic focus and 4 with remote stimulation in the AN. Three of 4 patients who had direct treatment had a decrease in seizure frequency (mean decrease 86%), and 2 of 4 patients who had remote treatment had a decrease in seizure frequency (mean decrease 74.3%).

These earlier systems usually consisted of recordings from chronically placed subdural electrodes and an external recorder and stimulator. However, rapid advances in computer and electronic technology have allowed the design of an implantable device capable of both recording and stimulation. The NeuroPace RNS system (NeuroPace, Inc.) is the first implantable closed-loop stimulator for epilepsy treatment. It is currently being evaluated for safety and efficacy in clinical trials. The RNS system monitors the patient’s electroencephalographic activity and automatically delivers electrical stimulation to the seizure focus (where the depth or strip electrodes are surgically placed) when the patient’s characteristic epileptiform activity is detected. The detection and stimulation parameters are set by a programmer. Preliminary results in 24 patients demonstrated at least a 50% decrease in seizure frequency in 43% of patients with complex partial seizures and 35% of patients with total disabling seizures (simple partial motor, complex partial, and secondarily generalized tonic-clonic seizures). Although these studies are promising, the question of whether closed-loop systems are superior to open-loop systems remains to be answered.

Patient Selection, Interdisciplinary Screening Teams, and Avoiding DBS Failures

Perhaps the greatest lessons we have learned in DBS are that patient selection is critical to success and that DBS must be tailored utilizing interdisciplinary screening teams to avoid treatment failures. The most exciting pearls from the epilepsy trials presented may be the observed failures. It is from the failures that we will learn the subsets of patients who may respond, the potential targets of therapy, and the approaches that will have the best chances at long-term success. The use of DBS in epilepsy, as in movement disorders, will need to move toward organization of interdisciplinary teams to screen, implant, and follow medication- and stimulation- or device-related issues. These teams will likely need representation from the fields of neurology, psychiatry, neurosurgery, neuropsychology, and in select cases from other members of the allied healthcare team. In addition, DBS boards for epilepsy will need to be convened to determine risk-benefit ratios for individual patients and to tailor therapy. We await the results of ongoing studies that will guide this process.

A criticism of most trials of DBS for epilepsy is that there is usually one arbitrary target chosen despite multiple seizure types (no tailoring). It is clear that such an approach is overly simplified, and it is from the lessons learned from DBS for movement and neuropsychiatric disorders that more tailored approaches should be implemented. In the largest controlled study of DBS for epilepsy, even though patients with a temporal lobe focus or focal had a significant reduction in seizure frequency, those with diffuse, frontal, occipital or parietal seizure foci did not have such benefit from such stimulation. In contrast, to date STN DBS seems to be more effective with seizures having a frontal focus or spread. Thus, it will be a tailored therapeutic approach that will likely win the day in epilepsy when the results of more clinical trials and basic science research are published.

A confounding factor in analyzing the efficacy of DBS for epilepsy is the fact that in most, if not all, patients enrolled in such studies numerous interventions (including resection of presumed seizure foci) have failed. Thus, these patients suffer from chronic epilepsy, which has been shown in both animal and human studies to result in rogue areas of secondary epileptogenesis. It is unclear how the stimulation areas and/or parameters would have to be changed if such treatments are used for more epileptically naïve patients. Also many trials have revealed the potential of a strong placebo effect or lesional effect with DBS.

Conclusions

Despite the weaknesses of existing studies, several trials of DBS for epilepsy have demonstrated improvement in seizure activity in patients with intractable epilepsy. These results are exciting and will drive further research into the ideal targets for certain types of epilepsy and patients. Particularly exciting have been the advances in scheduled and responsive stimulation. Elucidating the advantages of closed-loop versus open-loop systems (as being studied in the NeuroPace trial) as well as certain targets will provide tremendous potential options for patients with intractable epilepsy. The future of DBS as a curative versus palliative treatment will depend on how its outcomes compare with ATL and VNS. Anterior temporal lobectomy provides a cure for almost 60% of patients, who are seizure free at 1 year followup. In contrast, VNS is mostly palliative; it provides a reduction in seizure frequency of at least 50% in more than 50% of patients, but most patients do not become seizure free. Further studies will be necessary to determine which pa-
tients will derive a cure and which patients will have palliative reductions in seizure frequency.

The momentum for DBS in the treatment of epilepsy is quickly building with the recent SANTE trial and the FDA’s review for potential approval. The questions about the role of DBS in certain types of epilepsy and its potential side effects can only be answered by well-designed prospective studies.

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