Deep brain stimulation for epilepsy

Adrian Matthews (Meds 2013)
Faculty reviewer: Dr. Andrew Parrent, Department of Clinical Neurological Sciences, UWO

Introduction

Epilepsy is a chronic neurologic disorder characterized by recurrent, unpredictable seizures.\(^1\) It is estimated to affect 0.5 – 1% of the world’s population.\(^2\) Epilepsy is not a singular condition, but instead a diverse family of disorders with many causes, all of which indicate underlying brain dysfunction.\(^3\) This heterogeneity has important implications with respect to treatment regimens and patient responsiveness. About 35% of patients with epilepsy are refractory to anti-epileptic drugs, and of that group, only a quarter may benefit from resective brain surgery.\(^2\) Deep brain stimulation (DBS) may be a suitable treatment alternative for medically refractory patients who are not candidates for conventional surgical resection.

Procedure

DBS is a neurosurgical technique that uses electrical impulses to modulate or interrupt the inherent electrical activity of deep brain structures. Functional neurosurgeons use stereotactic MRI or CT scans to create a 3D coordinate system, allowing them to precisely locate anatomical targets and map out a suitable trajectory for reaching these targets.\(^4\) An electrode (lead) is implanted in the intended deep brain structure, and a battery-powered implantable pulse generator (IPG) is embedded in a subcutaneous pocket structure, and a battery-powered implantable pulse generator (IPG) is embedded in a subcutaneous pocket positioned inferior to the clavicle. An insulated extension wire that runs up the neck connects the two devices. The IPG is programmed to relay electric current to the lead, which then stimulates the targeted deep brain areas.\(^5\)

Since acquiring FDA approval for the treatment of essential tremor and Parkinson’s disease in 1997,\(^6\) DBS has been used for dystonia,\(^7\) and has shown promise in the management of Tourette’s syndrome, obsessive-compulsive disorder, and treatment-resistant depression.\(^8,9\) The success of DBS in treating movement disorders has prompted interest in the potential for DBS as a treatment alternative for medically refractory epilepsy.

Deep brain targets

A brief summary of selected deep brain targets that have been under investigation in animal and human models is presented here.

The substantia nigra pars reticulata (SNR) is known to be an important anticonvulsant site in rats. Pharmacologic animal studies have implicated the SNR as part of a ‘nigral control’ system for epileptic seizures.\(^10\) Since then, DBS of the SNR has resulted in seizure suppression in animal models, though no human trials have been published to date.\(^11\)

The subthalamic nucleus (STN) directly innervates the SNR, thus providing a rationale for using stimulation to interfere with this neural circuit and disrupt epileptogenesis.\(^12\) Small human trials have demonstrated at least 50% overall seizure reduction using STN DBS.\(^13-15\) Further studies are needed to clearly establish its clinical efficacy and to determine whether the optimal stimulation target is the STN or the SNR itself.\(^3\)

Temporal lobe epilepsy is common in adults and frequently does not respond to medical therapy.\(^2\) While temporal lobectomy is an effective treatment for certain patients, surgical resection is less desirable for patients whose seizures involve bilateral foci and who may suffer memory issues as a result of the operation. An alternative treatment, hippocampal stimulation, has been shown to be effective at reducing seizure frequency in patients with mesial temporal lobe epilepsy (MTLE).\(^16,17\) A double-blinded, randomized controlled study demonstrated a 15% median seizure reduction in four medically refractory MTLE patients for whom temporal lobe resection was contraindicated. No adverse effects were reported, and one patient had a substantial long-term benefit.\(^14\) Another double-blinded trial assessing hippocampal stimulation reported a 50-95% seizure reduction in certain refractory MTLE patients. It is worthwhile to note that this stimulation did not result in memory deterioration.\(^17\)

Stimulation of two thalamic structures, the centromedian nucleus (CM) and the anterior nucleus of the thalamus (AN), has provided encouraging results in human trials. The CM is involved in modulating cerebral cortex excitability, and its location between cortical, limbic and basal ganglia structures makes it an attractive target for disrupting epileptic neural circuits. Recent human trials using CM DBS have reduced seizure frequency by 80-95% in certain forms of epilepsy.\(^18,19\)

The AN’s anatomical connections suggest its potential as a vital target in the control of limbic epilepsy.\(^11\) Several animal studies have confirmed the AN’s role in seizure propagation,\(^20-22\) and recent human trials have reported seizure frequency reduction using AN DBS.\(^23-25\) Of considerable interest is the recently published Stimulation of the Anterior Nucleus of the Thalamus in Epilepsy (SANTE) trial: a controlled, randomized, double-blinded trial that examined data from 110 patients in 17 U.S. centres who received bilateral stimulation of the anterior thalamic nuclei. During the first 3 months (double-blinded phase), half the patients received active stimulation and half did not. Those that received stimulation had a median decline in seizure frequency of 40.4%, compared to 14.5% for the control group. Then all patients received unblinded stimulation for the remainder of the trial. After a two year follow-up, 54% of patients had their seizures reduced by at least...
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half, with 14 patients being seizure-free for at least 6 months.26

Complications

DBS is an advanced neurosurgical procedure. The accuracy required and complexity involved makes it prone to complications. Adverse events can be categorized according to those arising from the operation, the implanted hardware, or the electrical stimulation.27

The most severe operation-related complication is intracranial hemorrhage. While the risk from implanting a single lead is low, sometimes multiple passages are required to ensure proper electrode placement, increasing the risk of symptomatic hemorrhage. With an average distance of 8 cm from the cortical surface to most deep brain targets, utmost care must be taken to avoid major cortical blood vessels. Advances in imaging techniques, combined with thorough surgical planning, should help to ensure accurate lead placement with a minimal number of passages.27

Anchoring the electrode to the skull too tightly may fracture the device, causing a short circuit and draining the IPG battery. On the other hand, constant head and neck motions create traction that may cause a loosely attached electrode to migrate from its desired target. Infections around the anchorage site, the IPG site or the extension electrode to migrate from its desired target. Infections in the anchorage region may also complicate the procedure and necessitate removal of the entire system. Antiseptic cleaning procedures and prophylactic antibiotics may be used to curb this risk.27

Stimulation-related complications include confusion, depression, and mood changes. These may arise from malposition of the electrode. Indeed, many of the deep brain targets are very small, and a misplaced lead, even by a few millimetres, may cause unwanted side effects. However, these events are mostly reversible and adjustable, and no major stimulation-related events have been reported thus far.28

Open vs. closed loop stimulation

The majority of the trials referenced in this paper have described DBS protocols of scheduled stimulation, where electrical current is delivered either continuously or cyclically (alternating on-off phases). This technique, referred to as ‘open-loop stimulation,’ delivers current without reference to ongoing electroencephalogram (EEG) activity.11,28 Recent data, however, suggest that chronic stimulation of certain brain regions may exacerbate seizure activity.29 Cyclic stimulation may ease this effect, but it also appears to be less effective than continuous DBS at reducing seizure frequency.30

The protocol for using DBS to treat movement disorders is well-established.3 It relies on the concept of an epileptic brain fluctuating between a functionally normal state and an electrically abnormal one. Continuous stimulation in this context thus acts to reduce the brain’s excitability and maintain the functionally normal state. The stimulation parameters for using DBS to treat epilepsy have largely followed those for movement disorders; however, the optimal protocol of DBS for epilepsy has yet to be determined.31

An alternate strategy, called ‘closed-loop stimulation,’ uses real-time seizure detection algorithms designed to interpret characteristic EEG cues representing the onset of epileptiform activity, and deliver electrical stimulation accordingly. There is growing evidence that this type of adaptive stimulation may be effective in humans.31,32 The development of reliable automated detectors will be required to ensure this method’s feasibility.

Future directions

The success of DBS in treating motor disorders, along with its expanding potential in the management of numerous other conditions, including epilepsy, has “brought functional neurosurgery back to an exciting era.”27 To firmly establish the role of DBS for epilepsy, optimal stimulation parameters and deep brain targets must be defined for the various seizure types and syndromes. A better understanding of the mechanisms by which seizures propagate and how electrical stimulation has its effect will help to identify ideal surgical candidates and provide them with another therapeutic option worthy of consideration.

References

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