

Developments in Neurostimulation Therapy for Epilepsy

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Abstract

Neuromodulating neural tissue instead of performing lesions is a current trend in neurosurgery. In the case of epilepsy, stimulation of the nervous system is under investigation, and the field is growing at a fast pace. The purpose of this article is to review the various targets that have been studied in the search for a way to control refractory seizures. Consideration is made of why each target is chosen, patient selection, results, and adverse effects. Cerebellar stimulation was the first proposed method; vagus nerve stimulation is currently the most widely used due to its easy technique, but the results on seizure reduction are modest. Other targets were chosen with the idea of interfering with seizure propagation—this is the case with thalamic stimulation. Currently, studies are being performed stimulating the epileptic focus. Although there are still many controversies regarding which is the best target and stimulating parameters, all authors agree that neuromodulation reduces seizures and has the advantage of being reversible and safe.

Keywords

Neuromodulation, electrical brain stimulation, epilepsy, refractory seizures, stimulation anatomical targets, epilepsy surgery

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It is estimated that epilepsy affects approximately 50 million people worldwide.¹ Although conventional antiepileptic medications as well as newly developed ones have improved response in the majority of patients, it is known that up to 30% do not respond to appropriate therapy no matter how many antiepileptic drugs are administered.² These non-responsive patients are candidates for epilepsy surgery.

Many ablative procedures have been used, with differing results. Some procedures have excellent results, such as temporal lobectomy for mesial temporal epilepsy; others, such as callosotomy for generalized seizures or frontal resections for motor seizures, have poor results. Regardless of which procedure we choose, there are a number of patients who are not candidates for resective surgery due to several factors: poor seizure outcome with the chosen surgical procedure, failure to localize precise epileptic focus, bilateral or multiple foci, and high risk for post-surgical neurological deficits. In these circumstances patients are either excluded from surgery or surgery is performed partially with the risks of function loss and seizure persistence.

Brain stimulation has been proposed as an alternative surgical procedure that prevents resection of neural tissue. Instead of being removed or disconnected, tissue is stimulated in a programmed mode and 'taught' not to seize. For this purpose, special electrodes are used that are directed to different targets (for example the thalamus, cerebellum, or hippocampus). They are designed to remain within the stimulated target

permanently. They are connected through a subcutaneous extension to a subcutaneous pulse generator, which produces current that is delivered to the chosen target. With a portable computer we can turn the generator on or off, program it, choose the stimulation parameters (amplitude, frequency, pulse width, and other parameters), and change the stimulated contacts if desired. It is a reversible method.

The term 'stimulation' tends to be replaced by 'neuromodulation' since the mechanisms through which this method works are not necessarily excitatory or stimulatory—depending on the parameters used and the chosen neurological target, stimulation (excitation) or inhibition can be produced. Neuromodulation is not new; it has been used to control other neurological symptoms such as tremor and pain for a long time. Epilepsy is probably the most 'physiological' disorder of the nervous system that is known and, as such, a 'physiological' treatment is desirable. In 1973, Cooper³ reported a series of 34 patients with epilepsy who were treated with electrical stimulation of the paravermian cerebellar cortex; approximately 50% of patients had seizure reduction. Since then, a number of different targets (vagus nerve stimulation [VNS], thalamus, subthalamic nucleus, epileptic foci *per se*) as well as a variety of stimulation parameters have been used.

Cerebellar Stimulation

Since 1941, experimental studies^{4,5} have shown that seizure activity is abruptly terminated or modified by cerebellar stimulation. In 1980 Laxer

et al.⁶ reviewed the results of animal studies and concluded that the vermician and intermediate (superomedial surface) cerebellar cortex are more efficient for seizure control and that in generalized or focal epilepsy of the limbic system, seizures responded better. As mentioned above, Cooper reported his clinical results and since then several cases have been treated and reported in the literature. A review of different studies with a total of 129 patients showed that 49% had significant seizure reduction, with 27% being seizure-free. This and other studies⁷ have shown that the seizure type that best responds is the primary generalized tonic-clonic seizure and that there is an initial seizure reduction within the first two months of stimulation; not only is this effect maintained, there is a further seizure decrease with time.

Vagus Nerve Stimulation

The vagus nerve has projections to the thalamus, forebrain, and amygdala through the nucleus tractus solitarius and through the medullary reticular formation.⁸ Even though the precise antiepileptic mechanism remains unclear, it appears that these thalamocortical relay neurons modulate cortical excitability, influencing seizure generation or propagation. VNS has been used as a combination therapy in difficult-to-control seizures (either primary generalized seizures or complex partial seizures) in patients who are not candidates for ablative procedures. It is interesting that even though its effects on seizure reduction are modest (~30%), it is the only neuromodulation therapy for epilepsy that has been approved by the US Food and Drug Administration (FDA) to date. This is probably due to the fact that it is a simple procedure with minimal invasion, since reaching the vagus nerve at the neck level is relatively simple. It can produce dysphonia and headache, and increases peptic ulcer and insulin-dependent diabetes. It is not recommended for children under 12 years of age.

Centromedian Thalamic Nuclei Stimulation

High-frequency stimulation of non-specific thalamic nuclei (such as centromedian or anterior thalamic nuclei) interferes with propagation of cortical- or subcortical-initiated seizures, according to the centro-encephalic theory by Penfield and Jasper.⁹ In 1984, Velasco et al. performed the first bilateral centromedian electrode implantation in a 12-year-old boy with Lennox–Gastaut syndrome (and thus severe generalized seizures). The results in this first patient were very encouraging since there was a considerable seizure reduction and a very impressive improvement in his intellectual status. In 1987, the first report was published of children and adults with generalized seizures of the Lennox–Gastaut syndrome.¹⁰ Nevertheless, in 1992 a placebo-controlled pilot study¹¹ reported poor results using centromedian stimulation; the reasons for such a difference have since been studied.^{12,13} Centromedian stimulation does not work for all seizure types; it is more effective in generalized seizures and *epilepsia partialis continua*. The centromedian has different anatomical areas and the best results are obtained in the parvocellular portion. Anatomical definition is not enough and a neurophysiological definition of the target is needed. This definition is based on electrocortical responses elicited by stimulation of the electrode contacts within different zones of the centromedian nucleus. Two other important observations are that stimulation takes several months to gain its full effect and that, when stimulation is stopped, there is a ‘carry-on’ effect that prevents seizures from immediately reappearing. Today, the neuromodulation community

accepts the carry-on effect. When patient selection as well as the anatomical and neurophysiological criteria regarding target localization are optimal, the results are >80% seizure reduction; some patients can become seizure-free. An improvement in ability scales is also observed with no adverse effects.

Anterior Thalamic Nucleus Stimulation

As mentioned earlier, the anterior nucleus of the thalamus is a non-specific thalamic nuclei and, as such, interferes with propagation of cortical- or subcortical-initiated seizures.⁹ It also interferes with seizures initiated in mesial temporal structures and propagated through the fornix, mammillary body, and anterior nucleus of the thalamus.¹⁴ This nucleus has been stimulated in five patients for the treatment of partial epilepsy with secondary generalized seizures.¹⁵ It has shown significant improvement with respect to the severity and frequency of secondary generalized seizures.

Subthalamic Nucleus

Recently, the subthalamic nucleus has been stimulated for seizure control. A relatively small number of cases with various epileptic conditions have been treated. Improvement varies from 30 to 80% and seems to work better for seizures that initiate in the frontal lobe and myoclonic seizures.^{16,17} Mild facial twitching and paresthesias in legs and arms responded to adjustment of the stimulation parameters.

Electrical Stimulation of the Hippocampal Epileptic Foci

Mesial temporal lobe epilepsy constitutes the most frequent type of epilepsy referred to epilepsy surgery centers.^{18–20} Even though patients who undergo temporal lobectomy with amygdalectomy and/or hippocampectomy have very favorable outcomes, there are a number of patients who are not candidates for ablative surgery, such as those who have independent bilateral hippocampus foci confirmed with depth recordings, patients with short-term memory deficit, those with normal magnetic resonance imaging (MRI) with uncertain seizure lateralization, patients with epileptic focus localized in the posterior dominant hippocampus, and patients with high surgical risk often derived from toxic effects of antiepileptic drugs. Based on observations made by Weiss and her group,²¹ who observed that low-level direct current inhibits amygdala kindling in rats, in 2000 Velasco et al.²² published the first results of subacute hippocampus foci stimulation in 10 patients. These patients had undergone intracranial electrode implantation as part of their surgical protocol to localize the epileptic focus; once localized, a two- to three-week trial of subacute stimulation was delivered before performing temporal lobectomy. Seven of the patients became seizure-free from day six onwards. This publication allowed the performance of a number of neurophysiological and single-photon-emission computed tomography (SPECT) studies comparing basal conditions with post-stimulation conditions. Since patients underwent lobectomy, stimulated tissue was recovered and analyzed using high-performance liquid chromatography (HPLC) techniques. All studies suggested an inhibitory mechanism to explain seizure control.^{23,24} Long-term follow-up studies of hippocampal stimulation have been performed,^{25–28} with a favorable 50–100% seizure reduction. The best results are seen in patients with no hippocampal sclerosis observed on MRI scans.

Electrical Stimulation of the Motor Cortex Epileptic Foci

Ablation of the epileptic foci located in the supplementary motor or the primary motor cortices is performed in several epilepsy surgery centers.^{29–33} Although results vary within each center, the outcome of seizure reduction ranges from 65 to 100%. Most of the cases are patients who have lesions such as cortical dysplasia, cavernomas, and gliosis; very few non-lesional cases are included. The main problem with these surgeries is that there are a number of neurological sequelae: paralysis, paresis, apraxia, aphasia, and mutism. There have also been also complications due to the surgical procedure itself. If MRI is normal, the outcome is worse. Velasco et al.²⁰ investigated the anticonvulsive effect of cyclic, high-frequency stimulation of the epileptic foci located in the motor area in two patients with non-lesional intractable epilepsy, one of them in the right supplementary motor area and the other in the right primary motor area. Both had 95% seizure reduction without motor function impairment. This result is very promising, although conclusions cannot yet be drawn.

No matter which target is stimulated, which parameters are used, what results are reported, or what disagreements exist, all authors agree that neuromodulation is reversible and does not produce adverse events. If somehow a patient presents an undesirable effect, a change of stimulated contacts or parameters will eliminate the problem. No adverse effects on neurological function have been observed; on the contrary, function, and thus quality of life, tends to improve.

Currently, there are many studies of therapeutic stimulation for seizure control in progress. For example, detector systems are implanted for temporal and extra-temporal epileptic foci. These systems detect electroencephalography (EEG) activity to anticipate changes related to seizure onset and are coupled to a stimulation system that delivers electric current through an electrode placed on the epileptic zone. Initial

reports are promising, although challenges remain since seizure anticipation may depend on EEG activities that are not specific and therefore can provide false detections but, even worse, can miss seizure onset. Besides, in all neuromodulation trials it has been reported that the best anticonvulsive effects are reached after weeks and even months of continuous or cyclic stimulation. The field is immense.

Multidisciplinary work is encouraged; neurologists, epileptologists, neurophysiologists, neurosurgeons, and neuropsychologists need to interact and have close communication with basic scientists and biomedical engineers. The latter have shown great interest and texts are being elaborated in collaboration with neuromodulation investigators.¹ Questions need to be answered, new targets and different stimulation parameters need to be proposed, special electrode designs according to the stimulated target need to be elaborated, and smaller and less expensive stimulation systems that are better tolerated by patients need to be built.

However, the field to be explored does not end with all this. A more exciting phase is also being studied: the mechanisms that explain the therapeutic effect of neuromodulation. Being able to modify the way in which the brain works and to explain different circuits is intriguing. It all guides us to the main field of interest of all neuroscientists: how the brain works. ■

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