Epilepsy and Neurostimulation Therapy

A Review Article

A Review Article Submitted in Partial Fulfillment of the Requirements for the Degree of Bachelor in Medicine at University of Diyala

By

Noor Aziz

Supervisor

Dr. Asmaa Abbas Ajwad

2021-2022

Acknowledgement

First and foremost, I would like to express my sincere appreciation to my supervisor, Dr. Asmaa Abbas Ajwad, for her patience, insightful comments, and helpful information, all of which have been invaluable to me during my project.

My special thanks to the faculty of the University of Diyala /College of Medicine for everything they taught me as well as their encouragement and support.

Last but not least, I want to express my gratitude to my loving parents, who are the source of my strength and the reason I'm here today, and who continue to support me morally, spiritually, emotionally, and financially.

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ABSTRACT

Epilepsy and Neurostimulation Therapy

Epilepsy is a common, sometimes chronic, neurological disorder that carries health dangers as well as psychological and social implications that reduce quality of life. The treatment of epilepsy patients necessitates a long-term commitment on the part of both the general practitioner (GP) and the specialist. The most important prerequisites are a complete diagnosis, the selection of the best treatment, and personalized counseling. The majority of patients will go into remission and be discharged to their primary care physician, while the remainder will require ongoing treatment at the specialty clinic.

Medically refractory epilepsy is a type of epilepsy that is resistant to medical treatment in 30 to 35 percent of cases. For those who have a single focus for their seizures in the noneloquent cortex, resective surgery remains an underutilized yet extremely effective treatment. For those who are not candidates for resective surgery, neurostimulation which refers to the application of electricity to affect the central nervous system, with the goal of reducing seizure frequency and severity, is a less intrusive therapeutic alternative. Neurostimulation is gaining popularity as a treatment for drug-resistant epilepsy. Neurostimulation techniques classified into invasive and noninvasive modalities. The noninvasive techniques involve the transcranial application of electrical (direct or alternating) or magnetic fields to the scalp at subconvulsive levels. These interventions include repetitive transcranial magnetic stimulation (TMS), transcranial direct current stimulation (tDCS), and cranial electric stimulation (CES). Given the absence of an induced seizure, these interventions are hypothesized to act through plastic effects exerted by the repeated electrical stimulation of cortical circuits or via potentiation of endogenous firing (in the case of direct currents). The surgical approaches (invasive) involve the implantation of devices to chronically stimulate brain structures directly (as in lateral cerebral epidural electrical stimulation and deep brain stimulation (DBS) of deep targets) or indirectly (as in vagus nerve stimulation (VNS)). Surgical techniques, are thought to work by modifying firing patterns (via inhibitory, facilitatory, or modulatory actions).

In this article, we give a brief summary of available neuromodulation therapies, including vagal nerve stimulation (VNS), deep brain stimulation (DBS), and responsive neurostimulation (RNS) (RNS).

Introduction

Epilepsy is one of the most common neurological illnesses, affecting 1-3% of the global population. First, we would like to distinguish between two commonly used terms: epileptic seizures and epilepsy, as many people are confused about them. The excessive, hypersynchronous discharge of neurons in the brain causes a "seizure," which is a paroxysmal disruption of neurologic function. The term "epileptic seizure" is used to distinguish between a seizure caused by abnormal neuronal firing and a seizure that is not caused by abnormal neuronal firing, such as a psychogenic seizure. Recurrent, spontaneous seizures are referred to as "epilepsy" which can be caused by a variety of factors, each of which reflects underlying brain dysfunction[1][2]. In 2005, the International League against Epilepsy (ILAE) defined epilepsy as a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures and by the neurobiological, cognitive, psychological, and social consequences of this condition. The definition of epilepsy requires the occurrence of at least one epileptic seizure. About 1% of the population suffers from epilepsy, and about one-third of patients have refractory epilepsy (i.e., seizures not controlled by two or more appropriately chosen antiepileptic medications or other therapies). Approximately 75% of epilepsy begins during childhood, reflecting the heightened susceptibility of the developing brain to seizures [1][3].

Epileptic seizures arise from an excessively synchronous and sustained discharge of a group of neurons. The single feature of all epileptic syndromes is a persistent increase of neuronal excitability. Abnormal cellular discharges may be associated with a variety of causative factors such as trauma, oxygen deprivation, tumors, infection, and metabolic derangements. However, no specific causative factors are found in about half of the patients suffering from epilepsy [4]. Underlying causes and pathophysiological mechanisms are (partially) understood for some forms of epilepsy, e.g. epilepsies caused by disorders of neuronal migration and monogenic epilepsies.

There are three types of seizures: generalized, focal (also known as partial), and epileptic spasms. Focal seizures are caused by neural networks that are exclusive to one hemisphere of the brain. Bilateral distributed neural networks are the source of generalized seizures. A focused seizure can progress to a generalized seizure. Seizures can start in the cortex or in the subcortical areas. A clinician can often categorize the seizure/epilepsy type based on a detailed history, EEG findings, and supplementary information[1].

The removal of the underlying cause is the primary therapeutic technique for epileptic seizures. Drug therapy is used to control the majority of epileptic seizures. The sort of treatment suggested will be determined by a number of factors, including the person's age, overall health, and medical history, as well as the frequency and severity of the seizures. The most common types for epilepsy treatment include: Pharmacological treatment, ketogenic diet, surgery, and brain stimulation. In this article, we are going to focus on brain stimulation technique for epilepsy treatment, specifically responsive neurostimulation (RNS) that doesn't require the surgical removal of brain tissue and uses an implanted device to help prevent seizures before they begin, similar to how a pacemaker detects and treats abnormal heart rhythms.

Neurostimulation Modalities

The use of electricity to stimulate the central nervous system with the purpose of reducing seizure frequency and severity is known as neurostimulation. Though the concept has been around for more than a century, neurostimulation has grown in popularity since the United States Food and Drug Administration (FDA) approved vagus nerve stimulation (VNS) in 1997. There are a variety of techniques available, ranging from non-invasive to invasive. Some studies focus on the seizure-onset zone (SOZ) for a specific patient, while others look at more general areas that are considered to affect seizure-related neuronal networks. Some devices are open-loop, while others sense brain activity and administer stimulation based on identified events (closed-loop) [5].

The majority of today's neurostimulation devices are open-loop, meaning they administer continuous stimulation in a pre-defined pattern without providing feedback. RNS, on the other hand, is a closed-loop system, which means that stimulation is only provided when the device detects particular conditions. More modern VNS versions include a sensor component that provides stimulation when tachycardia is present. Closed-loop stimulation is hypothesized to function by aborting seizures in real time, or at the very least responding to seizure-related electrical activity, lowering the amount of time patients spend in high-risk states. Open-loop stimulation, on the other hand, may affect all states, not just seizure-prone ones, lowering seizure risk overall[6][7][8].

This article explains some of neurostimulation techniques such as vagal nerve stimulation (VNS), deep brain stimulation (DBS) and responsive neurostimulation (RNS) which is the topic we will explain it in details because of its effectiveness in controlling epileptic seizures comparing to other modalities.

Vagus Nerve Stimulation (VNS)

In 1997, the US FDA approved vagus nerve stimulation (VNS) for persistent focal epilepsy, and it is now allowed for children aged four and up. In pediatrics, it is the most researched neurostimulation modality. A cuff is looped around the vagus nerve and attached to a VNS generator, which is usually implanted just beneath the pectoral muscle, see figure 1. To avoid any stimulation of the sinoatrial node, which gets input from the right vagus nerve, the left vagus nerve is usually chosen. According to clinical investigations, cardiac effects from right-sided vagus nerve activation are usually minimal. VNS allows patients or their family to activate stimulation by swiping a magnet across the device, in addition to pre-defined continuing stimulation sequences .VNS devices have been implanted in over 100,000 people throughout the world to treat epilepsy. The nucleus tractus solitarius (NTS) and its downstream projections to the limbic system and thalamus are thought to moderate hyperexcitable brain areas by boosting activity in the nucleus tractus solitarius (NTS) and its downstream projections to the limbic system and thalamus. The NTS then projects to the locus coeruleus and raphe nuclei, where VNS stimulates the synthesis of norepinephrine (NE, also known as noradrenaline (NA)) and serotonin, both of which have antiepileptic effects [6][5](Brain Sci. 2019, 9, 283) .

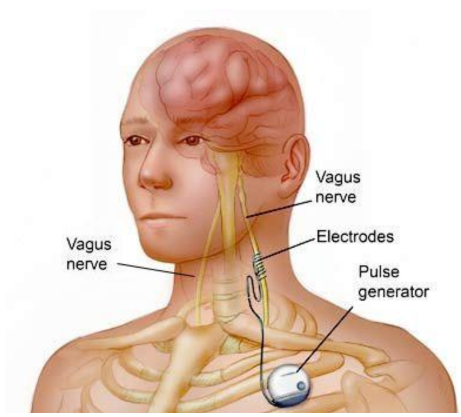

Figure 1: Vagus Nerve Stimulation (VNS) technique. The VNS sends low and repeating pulses of electrical current through the vagus nerve to the brain. It operates regardless of seizure warning signs.

Deep Brain Stimulation (DBS)

Deep brain stimulation (DBS) was approved by the FDA in 2018 for the treatment of intractable epilepsy in patients aged 18 and up, based on the findings of the Stimulation of the Anterior Nucleus of the Thalamus for Epilepsy (SANTE) trial, which showed adult patients prospectively followed for five years and showed a median percent seizure reduction of 69 percent. A permanent generator is implanted superficial to the pectoral muscle for stimulation of the anterior nucleus of the thalamus (ANT) DBS, and electrodes are put in the bilateral ANT. The centromedian nucleus of the thalamus (CMT), the subthalmic nucleus (STN), the globus pallidus, the cerebellum, the hippocampus, the caudate nucleus, and the seizure onset zone itself have all been identified as potential targets. The CMT has been designed to help those with generalized epilepsy. Li and Cook recently evaluated three modest (maximum sample size N = 9) randomized-controlled trials of hippocampal stimulation for mesial temporal lobe epilepsy, all of which showed a reduction in seizure frequency (15–40%) compared to placebo. During unblinded follow-up, all patients in the bigger study showed a >50% reduction in seizure frequency (Brain Sci. 2019, 9, 283). The mechanism of DBS is unknown, but it is thought to interrupt seizure propagation networks. The ANT is a key node in Papez's limbic circuit. The specific mechanism by which this effect is mediated is unknown—DBS does not "lesion" the target area and the relative neuromodulatory or neuroinhibitory effects are dependent on stimulation parameters. Stimulation of the ANT and CMT can cause widespread responses on scalp EEG and decrease interictal discharges, showing that thalamic stimulation has an impact on diffuse network activity[9][6].

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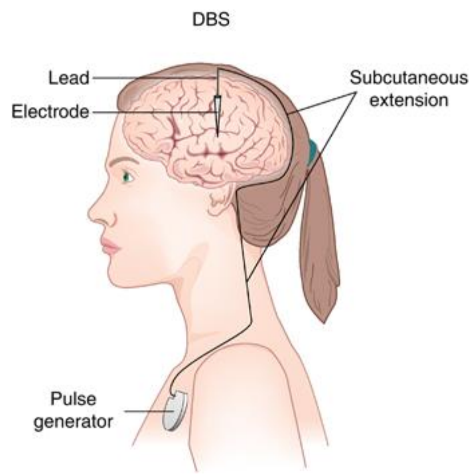

Figure 2: Deep Brain Stimulation (DBS). neurostimulator sends electrical impulses to the brain. The electrical impulses travel through leads to electrodes, which are implanted, (placed) in the anterior nucleus of the thalamus (ANT), a part of the brain that is involved in the spread of seizures.

Responsive Neurostimulation (RNS)

A responsive neurostimulation (RNS) device is a closed-loop device that delivers targeted stimulation to the putative seizure onset zone. Unlike the other methods of neurostimulation, RNS was designed to abort seizure activity. It is used for treating focal epilepsy. (Focal epilepsy used to be called partial epilepsy.) The goal of RNS is to disrupt unusual electrical signals in the brain that trigger seizures. The RNS System is used in conjunction with drugs in individuals 18 years of age or older with partial onset seizures who have undergone diagnostic testing to identify up to two areas of the brain where seizures originate and have not responded to two or more antiepileptic medications. A stimulator is implanted and one or two wires are placed at the location in the brain where seizures start. When the unit detects patterns that could lead to a seizure, it sends electrical signals to interrupt a seizure before it begins. RNS may be an option when medications aren’t able to control symptoms [7].

In 2013, the FDA approved RNS (NeuroPace, Inc., 455 N Bernardo Ave, Mountain View, CA 94043, United States) for the treatment of people with focal drug-resistant epilepsy. Bergey et al. reported a two-year, blinded, randomized, and controlled experiment that showed a 53 percent reduction in seizure (Keith Starnes).

The RNS system is implanted under general anesthesia and normally takes 2-4 hours to complete. Many patients can go home the next day, while others can expect to stay in the hospital for 1-3 days. After surgery, there is no need for bed rest, and many patients are able to resume normal activities within a few days, and even return to work within 2-4 weeks.

Components of RNS Device

It consists of delivering stimulation to intracranial electrodes to localize brain function, see figure (3). Following that with stimulation, the after discharges are stopped and seizures are avoided. When compared to functional mapping, RNS gives electrical stimulation based on detected patterns but with a shorter pulse and lower current activity[10]. At the seizure focal, one to two leads with four contacts each are inserted subdurally or as depth electrodes. The leads are attached to a stimulator implanted in the skull. The connections can be set up as anodes or cathodes, and the stimulator can also function as a cathode. Patients are given a programmer, which is in the form of a laptop attached to a wand. Patients use the wand to download ECoG data onto an internet database for physicians to review after a seizure (Alendia, Nilika). The epilepsy providers tailor the stimulation to detect seizure ECoG patterns using this recorded data. The implanted electrodes' patterns can then be configured to produce up to five bursts of electrical stimulation

(0.5–12 mA) lasting 100–200 ms each (Figure 4). Thousands of times per day, this stimulation takes place.

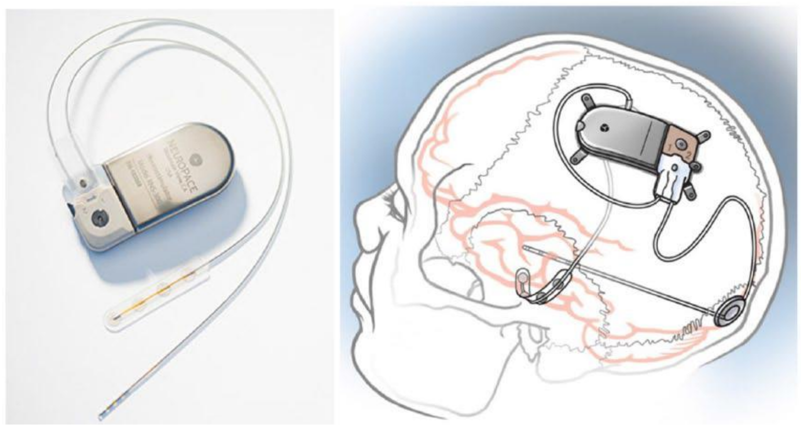

Figure 3: Responsive neurostimulator (RNS): the top left image is the stimulator attached to subdural and depth electrodes; the top right diagram shows placement of the stimulator in the skull

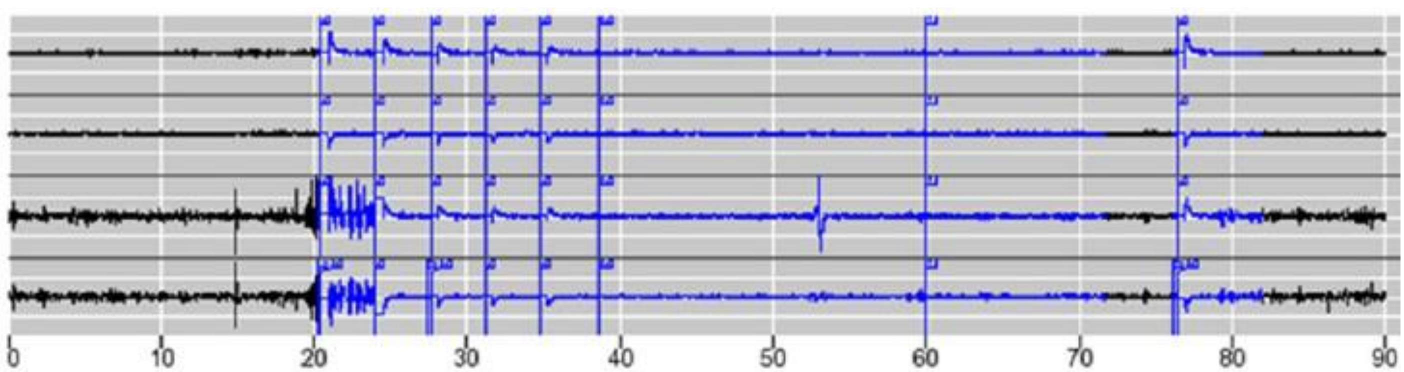

Figure 4: Detection of preprogrammed ECoG (electrocorticography) pattern followed by a train of five electrical stimulations which aborts the ECoG pattern.

Advantages and Disadvantages of RNS

The following are some of the benefits of RNS: Reduced stimulation level not only helps the battery survive longer, but it also reduces the possibility of long-term continuous stimulation side effects [5], [7], [10]. Most importantly is that the stimulation is targeted only at the seizure focus. On the other hand, the disadvantage of RNS device include the following: It is expensive ($35,000 and $40,000), implant surgery is required, and chronic power replacement (2-3.5 years). There are some risks associated with it. Infection risk has been estimated to be 3.7 percent per surgery. Intracranial bleeding was recorded in 4.7 percent of surgeries, and lead damage was documented in 2.6 percent. Other non-implant-related problems are uncommon, and there was no significant difference in adverse events between the sham and treated groups. The rate of serious adverse events is comparable to other intracranial implants or epilepsy surgery. MRI compatibility is not currently available for the RNS system. No significant impact of mood or cognition has been seen in studies, and some patients have reported improvements[5], [7], [10].

Patient Responsibilities with RNS

Patients who pick the RNS system for therapy play an important role in their own care. Each patient is given a remote display, which is effectively a laptop computer, to which they must daily download the information from their neurostimulator. This procedure only takes a few minutes each day. They are required to upload the data from their remote monitor to a secure online database once a week so that their doctors can review it. When a patient has a seizure, they are given a magnet and instructed to swipe it over their neurostimulator. This action designates that particular incident as significant, and the device saves the recorded brain activity so the doctor can investigate further [9], [10].

Conclusions

Millions of individuals throughout the world suffer from epilepsy. Families, physicians, researchers, and, of course, the government must all work together to combat the disorder. A combination of research methodologies could result in a better knowledge of therapy effects and more realistic epilepsy management.

Neurostimulation is a promising new therapeutic option for persons with epilepsy who aren't candidates for surgical resection and whose epilepsy isn't responding to medication. The efficacy of various approaches is unknown because an effect can be temporary or permanent. Although there are no direct comparisons or head-to-head tests available, each technique offers benefits and drawbacks. Multiple approaches can be combined to achieve seizure control, and the decision to adopt a certain form of neurostimulation should be decided within a multidisciplinary team approach. In the future, a method of assessing seizure probability in real-time may allow for more reasonable stimulation setting selection. This would be facilitated by a better knowledge of the mechanisms of action as well as the identification of neuromodulatory response biomarkers.

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