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# Brain Stimulation for Seizure Control: Considerations and Potential Mechanisms

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## 1. Introduction

Attempts at nervous system electrical stimulation (a.k.a., brain stimulation, neurostimulation, electrical stimulation, neuromodulation, or deep brain stimulation (DBS)) have been made to treat drug-resistant forms of movement disorders and other conditions such as chronic pain, major depression, and more recently, seizure disorders (Theodore and Fisher 2004; Theodore 2005). Experimental results in some cases have been promising and DBS, a form of electrical stimulation, has been approved (2002) by the Food and Drug Administration (FDA) as a treatment for Parkinson's Disease.

Recent lab and clinical data also suggest that electrical brain stimulation in central and peripheral nervous system targets reduces seizure frequency in epileptic patients and in animal models of recurrent seizures (Cooper, Upton et al. 1982; Engbaek, Ostergaard et al. 1989; Benabid, Pollak et al. 1991; Brusa, Pierantozzi et al. 2001; Benabid, Minotti et al. 2002; Vitek 2002; Lang, Kleiner-Fisman et al. 2003; Vonck, Boon et al. 2003; Benabid, Wallace et al. 2005; Boon, Vonck et al. 2007; Velasco, Velasco et al. 2007; Arai, Yokochi et al. 2008; Montgomery and Gale 2008; Aybek, Lazeyras et al. 2009; Baumer, Hidding et al. 2009; Berweck 2009; Boon, Raedt et al. 2009; Rezai 2009). These findings may seem counter intuitive given the fact that electrical stimulation in the nervous system has been used in many cases to excite neurons, or to replace a lost function following injury. Nevertheless, electrical stimulation under certain conditions has been shown to reduce seizure activity. For example, in the peripheral nervous system, vagus nerve stimulation (VNS) has been performed in humans for many years (FDA approved 1997) where clinical studies show reductions in seizure frequency (Woodbury and Woodbury 1990; Vonck, De Herdt et al. 2009). More recently electrical stimulation of the central nervous system has been attempted to treat epilepsy in both animals and humans where animal studies have varied in efficacy and human studies, although very promising, have not always been well designed or controlled.

Neurostimulation for seizure control typically involves the stimulation of brain structures that can be conceptually divided into three groups. These include structures that are: 1)

directly involved in epileptic activity, such as the hippocampal formation, 2) white matter tracks, which are connected to epileptogenic regions, or 3) deep brain structures, such as the subthalamic nucleus.

However, in spite of the fact that brain stimulation has been utilized in clinical settings in humans, no mechanism for neurostimulation has yet been substantiated with sufficient evidence. In addition, more work is needed to elucidate targets and electrical parameters for optimal delivery, such as stimulation frequency and mode, etc.

This chapter will cover the key points of neurostimulation and also some of the unresolved aspects of neurostimulation in epilepsy, namely targets for stimulation, parameters of stimulation, and potential mechanisms associated with stimulation. It will primarily focus on aspects of CNS neuromodulation. It will conclude with interesting highlights from two clinical trials, both of which are currently ongoing and to date have shown positive results. Finally, some brief discussion will be made concerning future directions of neurostimulation.

## 2. Targets for stimulation

Electrical stimulation has been attempted in several regions of the brain and includes the hippocampal formation, cerebellum, caudate nucleus, centromedian thalamus, anterior thalamus, subthalamus, and neocortical regions, to name a few (Table 1). However, the best structures to stimulate and the most effective stimulation protocols to use in each target are still a matter of debate and are under investigation (Theodore and Fisher 2004). As mentioned above, these targets can be subdivided conceptually into several categories including: direct focal targets (ie., epileptogenic zone), deep brain nuclei, and white matter tracts.

More specifically, one approach that has been taken with white matter tract stimulation is to stimulate a white matter tract that is connected to the majority of the neurons in the epileptic zone. For example, stimulation of the corpus callosum or the fornix has been accomplished with the hope that by applying supramaximal stimulation intensity to these tracts that epileptogenic activity can be completely blocked (a.k.a., overdrive stimulation) (Luders, Najm et al. 2004). The rationale for using supramaximal intensities is that at this level of intensity it appears unlikely to elicit additional epileptic seizures. Pilot animal studies thus far using bilateral stimulation of the fornix have been encouraging, but are limited in number.

With regard to direct stimulation of the epileptic zone, cortical and hippocampal targets have been the most common targets explored thus far. In particular, hippocampal sclerosis is one of the most common forms of epilepsy where these patients are frequently not surgical candidates due to concerns about potential memory deficits following surgery. Therefore, it is hoped that electrical stimulation of the hippocampus might be developed as a viable therapeutic alternative for these individuals. To date, small clinical trials by Velasco et al. (Velasco, Velasco et al. 2000; Velasco, Velasco et al. 2000; Velasco, Velasco et al. 2007) have been performed and have showed promising results, however these studies were not double-blinded in design and so more work is needed in this area.

Several deep brain structures have also been targeted. These include the caudate nucleus, the posterior hypothalamus, the thalamic nuclei, and the subthalamic nuclei. Among these targets, recent studies appear to favor the thalamic and subthalamic nuclei (STN). Interestingly, in the early 1980s the nigral control of epilepsy system (NCES) was described

(Iadarola and Gale 1982) where the STN seems to play major role in this system. Past studies indicated that abnormal activity in the STN was a main feature in the pathology of movement disorders. However, more recently the role of the STN in epilepsy has been investigated and targeted with DBS stimulation protocols.

## 3. Parameters of stimulation

There are a number of variables that are important to consider when attempting to understand the parameters associated with neurostimulation. These include the basic physical properties and relationships such as *energy sources, voltage, current, resistance, capacitance, and fields*, etc. An exhaustive discussion of these properties and relationships is not the focus of this chapter and there are many excellent references that can be examined in this regard (see (Feyman, Leighton et al. 1977)). Our consideration will be qualitative for the most part. One fundamental relationship to briefly present in this context is of course, Ohm's law, $V = IR$ or $R = V/I$. In this relationship, *resistance (R)* measures the magnitude of *voltage (V)* across an element when passing the circuit *current (I)*. We introduce this concept since neurons and glial cells of the brain have resistive properties. Similar to resistance we can think of another property, that of *resistivity* ($\rho$), which takes into account a current flowing through a cross-sectional area (such as a fiber tract). The reciprocal of resistivity or $1/\rho$ is the *conductivity* ($\sigma$). It is often more intuitive to think in terms of conductivity when analyzing ion channel function in the nervous system.

In addition, one needs to consider the location of the stimulation electrodes, the strength and duration of a stimulus, the geometry of the target being stimulated, and other electrical characteristics of the target tissue. When analyzing the geometry of potential nervous system targets, there are two shapes that are typically used as models, that is, a spherical cell and a cylindrical fiber. For a quantitative description of these models several resources are suggested for additional reading (Plonsey 2008). In actual biological systems, cells and tissues are considerably more complex than simple spheres or cylinders, but this geometry serves as a useful starting point for our discussion.

For example, an external device such as a stimulator delivers current to the target cells and creates a rising transmembrane voltage, which at first is subthreshold (ie., a graded potential) when delivered at low intensities. In this simplistic model, the transmembrane potential will be nearly uniform at all points on the cell membrane and the entire membrane will respond in a similar manner. However, fibers are evaluated using stimuli placed in different locations along the length of the fiber and require additional considerations. Another perspective that is helpful is to think of action potentials propagating along a cylindrical nerve fiber, which has an excitable membrane. In this scenario, each patch of excitable membrane initiates the transfer of a packet of energy to adjacent patches of excitable membrane. Classic cable theory has been applied to nerve fibers to mathematically describe the propagation process (Plonsey 2008) more precisely. In addition, the reader is referred to standard neurophysiology texts (Kandel, Schwartz et al. 2000) that discuss the well documented permeability changes that involve sodium and potassium flux, etc. One other noteworthy point regarding geometry is that the orientation of nerve cells relative to the voltage field (ie., voltage gradient) is important since those cells in the direction of the voltage gradient will more likely be activated than those cells lying along an isopotential line.

In addition, neurostimulators are either monopolar or bipolar in configuration. Depending on which type is used will determine the current density around the electrode, how easily some cells are activated, and which population of cells is activated. In general, nerve cells that are nearer the electrode will more likely be stimulated. However, axons will be stimulated at lower stimulation intensities than nerve cell bodies. In addition, larger axons will respond to lower stimulus intensities than will smaller axons. Also, axons with multiple branches will be more easily activated than axons without branching processes.

Other programmable parameters that neurostimulators utilize for neuromodulation include voltage, pulse width, cycle on and off times, ramping, duration, and frequency. The combination of these parameters is critical for maximum efficacy. For example, both low and high frequency stimulation protocols have been attempted for seizure control. Historically, low frequency protocols (1 Hz), have been used in neurophysiological experiments involving synaptic plasticity and memory. In particular, 1 Hz stimulation in many circumstances resulted in so-called, long-term depression (LTD), a molecular correlate of memory associated with amnesia and forgetting. Because, LTD also leads to decreases in neuronal excitability, it has been postulated that low frequency protocols around 1 Hz should be effective in reducing seizure frequency. However, the evidence to date shows mixed results in this regard. For example, Weiss et al. demonstrated that the application of 1 Hz (15 min.) to the hippocampus or amygdala following a so-called kindling stimulus (60 Hz for 1 sec once daily) produced a long lasting suppressive effect on seizure activity (Weiss, Li et al. 1995). However, in a follow-up study by the same lab, it was reported that the stimulators that were used in the original study emitted an unexpected low level (i.e., 5 – 15 μA) direct current, which was suspected to have a significant effect on the inhibition on seizure activity (Weiss, Eidsath et al. 1998). Substantially more experimental work has actually been accomplished to date in both animal models and in human trials using higher frequencies of stimulation (ie., around 130 Hz) for seizure control. Overall, frequencies from 0.1 to 450 Hz have been tried in both animals and humans with various results (Rise 2004; Albensi, Oliver et al. 2007).

One other aspect is worth mentioning. Stimulation can be applied using either open loop or closed loop systems (Li and Mogul 2007; Pollo and Villemure 2007). Closed loop is defined as the delivery of electric current to a target, exclusively in response to a prompt. This type of delivery would be defined by a computer algorithm, whose onset is triggered by a seizure detection device. An example of open loop stimulation would be any stimulation protocol that is delivered independently of the time of occurrence between seizures.

Finally, a mention of safety issues is also appropriate. Early attempts in electrical stimulation resulted in some deleterious results. For example, repeated applications of direct current caused tissue injury, which was reversed if one used charge-balanced pulses instead. In other words, a stimulus protocol that utilizes two phases of current flow (positive and negative phases) resulting in a net charge flow of zero proved optimal and is now the standard method for pulse delivery. Other experimental attempts have resulted in the realization that only delivering limited levels of charge density per phase are essential so that the overall risk of injuring tissue is minimized. Some infections near the site of electrode implantation have also been reported, however, these occurrences are

quite low and have not been serious. There are also some concerns when using DBS in a MRI context and some cases have been where excessive heating of the implanted electrodes has been an issue (Sharan, Rezai et al. 2003; Coffey 2004; Rezai, Phillips et al. 2004)

## 4. Mechanisms of stimulation

As of this writing, mechanisms for DBS or VNS are not known. Several theories have been put forward for nervous system studies involving electrical stimulation in general, and for DBS and VNS in particular. For example, some speculate that prolonged electrical stimulation "jams" neuronal circuits (Greenberg 2002); however, this explanation is vague from a neurophysiological point of view. Slightly more developed theories (Pollo and Villemure 2007; Shapiro, Vaillancourt et al. 2007; Montgomery and Gale 2008) have proposed mechanisms involving "inhibition of synaptic transmission", a.k.a. the neurochemical hypothesis, or "depolarization blockade", a.k.a. the electrical hypothesis, but substantial evidence is lacking in both regards and these ideas have not yet been thoroughly substantiated in experimental models.

Interestingly, the effects of neurostimulation are known to change with the frequency of stimulation and also with the duration of the pulse or train of stimulation. This implies that stimulation at any particular target may attenuate seizures with some electrical parameters and induce seizures with other parameters. Evidence to date also supports this notion; for example, it is well known that kindling protocols (Fisher 1989; Weiss and Post 1998; Albensi, Oliver et al. 2007) are used to indirectly induce epilelptiform activity in intact animals. It should also be realized that there may be several mechanisms responsible for efficacy – not just one, which makes the investigation of mechanisms more complex than perhaps originally thought.

There is also one other concept that is often brought up when one discusses potential mechanisms of action and that is the idea of remote control versus direct control (Pollo and Villemure 2007). Central to this idea, electrical stimulation of specific circuits in cortical and basal ganglia networks appear to result in different levels of control depending on which brain region network is being targeted. In other words, targeting the area of epileptiogenesis (ie., seizure focus) with neurostimulation is called direct control. Whereas, electrically stimulating one of the intermediate relays or fibers in some circuit that connects to the epileptic zone is considered remote control. Examples of remote control include neurostimulation of the dorsal midbrain anticonvulsant zone (DMAZ), anterior thalamic nuclei, white matter tracts, and the centromedial thalamic nuclei. An example of direct control would be electrical stimulation of the hippocampus. Both approaches have shown efficacy and are active areas of investigation to determine which approach may be more effective.

## 5. Recent studies

Over the last several months promising human data has been published by Fisher et al. showing that electrical stimulation of the anterior nucleus of the thalamus reduced seizure frequency in individuals with refractory epilepsy (Fisher, Salanova et al. 2010). This ongoing

study was prospective, randomized, parallel, and double-blinded in design. One hundred and ten patients were randomized at the start of the trial. Those treated were adults with refractory partial seizures, including subjects with secondarily generalized seizures. In this study, at least three anti-seizure drugs must have failed to produce seizure control prior to baseline in order to be eligible for inclusion. At baseline seizure frequency was approximately 19.5%. At the time of this writing the study is over two years old. During months 1-4 of the trial, all participants were blinded where one-half received stimulation (typically using 145 Hz) and the other one-half received no stimulation. In the last month of the blinded phase (ie., month 4) the stimulated group had a 29% greater reduction in seizures compared with the control group ($p=0.002$). By two years, there was a 56% median percent reduction in seizure frequency. Interestingly, participants showed no group differences in mood or cognition, but those in the stimulated group were more likely to report problems with memory or depression. Overall, it was concluded that bilateral stimulation of the anterior thalamus was effective at reducing partial and secondarily generalized seizures.

In yet another recent study, a multi-center, prospective, randomized, double-blinded, sham controlled trial of individuals 18 to 70 years of age with medically intractable seizures for 3 months or more and localized to one or two foci is underway (Spencer, Gwinn et al. ; Skarpaas and Morrell 2009). In this trial, one-hundred and ninety-one subjects were recruited in order to test a cranially implanted programmable responsive neurostimulator (NeuroPace, Inc.). This device was used for treating partial onset seizures with or without secondary generalization. To be eligible for inclusion, subjects had to have failed 2 or more antiepileptic medications. One month following implantation, subjects were randomized 1:1 to receive sham or active responsive stimulation. In this study, the neurostimulator was programmed to acquire data on seizure detection. Stimulation was then delivered at the time and site of detection (eg., mesial temporal structures - hippocampus), before seizure spread or before any overt symptoms appeared. In other words, the system is designed to detect abnormal electrical activity in the brain and to deliver electrical stimulation to suppress seizures before there are overt seizure symptoms. Subjects were blinded to their treatment for 3 months. During this blinded period, neurostimulation was shown to significantly ($p=0.012$) reduce the number of seizures per day by 37.9% as compared to 17% in the untreated arm. After three months of blinded treatment the individuals were allowed to continue in the study in an open label manner. Some complications were seen from treatment, such as implant site infections and intracranial hemorrhage, but these side effects were relatively low in frequency.

## 6. Future directions

The use of neurostimulation for nervous system modulation is rapidly increasing. The success of this therapy, however, is far ahead of our understanding of the mechanism(s) associated with neurostimulation. It is also important to remember that early success using neurostimulation techniques occurred with technology that was not specifically fabricated for the current applications. In other words, only recently have the medical devices used for neurostimulation been designed and tailored for their present use and so it is possible the field may soon witness unprecedented growth given improved technology in the future.

One past limiting factor has been the ability to predict and detect seizure onset. Much work is still needed in this regard, but some very recent advances have been made (see discussion above concerning the NeuroPace trial). How to determine when a seizure will begin remains one of the great unanswered questions in epilepsy. Without a doubt, this limitation is a serious one, but once overcome, we will greatly advance the implementation of technology for responsive forms of neurostimulation. Advances in signal processing and detection devices will most certainly help in this regard.

It should also be noted that other technologies are being developed in parallel and may profoundly influence the field of neuromodulation therapy in epilepsy and other CNS disorders. For example, transcranial magnetic stimulation is also under development and has been shown to noninvasively interfere with neural activity. In particular, low frequency repetitive transcranial magnetic stimulation appears to temporarily improve intractable epilepsy. At this time, it is hard to predict if and how this technology may or may not advance in unison with techniques that involve the chronic implantation of electrodes.

From a neurobiological point of view it is hard to believe that repetitive stimulation has no effect on the genome. The truth is we do not know if it does or does not and to date very little research has been accomplished to explore this possibility. Future studies are warranted that would profile gene expression at various frequencies and other conditions to determine the long term effects of electrical stimulation on cell physiology.

Interestingly, attempts at using DBS in obesity have resulted in some unexpected results. In a recent study by Lozano et al. (Hamani, McAndrews et al. 2008), physicians were attempting to treat a morbidly obese man using DBS and found that electrical stimulation of the hypothalamus/fornix caused the patient to experience vivid memories. The individual suffered from type 2 diabetes and also sleeping disorders and failed to respond to other forms of treatment for these conditions. DBS for treating obesity is very new and only a few attempts have been made in this regard. Following surgery the patient recovered for two months, and later when the implanted electrodes were stimulated once again, he experienced the recollection of more memories. These results suggest that DBS might be a viable alternative for those with memory disorders; in particular, for those with Alzheimer's disease (AD). To this end, Lozano and colleagues are currently conducting a pilot study in AD patients (Laxton, Tang-Wai et al.) where 6 patients are being treated with this therapy. Data from this study suggested that DBS treatment in hippocampal areas resulted in an early and striking reversal of impaired glucose utilization in temporal and parietal lobes (as measured by PET scans) that was maintained after 12 months of continuous stimulation. These data are so new and unexpected and the sample sizes are so low, that it is important to add a note of caution in association with these studies. Regardless of the studies' limitations, further work is warranted to investigate these very preliminary, but exciting findings.

It is also expected that scientists and physicians from a variety of disciplines, such as bioengineering, computer science, neurophysiology, neurology, and psychiatry, etc. will work together more cohesively than in the past in order to advance the field of neurostimulation; this will be important with regard to understanding mechanisms of action, advancing technology, and improving the quality of life of epilepsy patients and others with serious CNS disorders.

In any case, it should be obvious that we are witnessing a new horizon with promising results thus far and unimaginable rewards and outcomes yet to come.

| Target Stimulated | Proposed Pathway and/or Mechanism | Efficacy |
|---|---|---|
| **Cerebellum** | Direct anterograde cortical inhibition or stimulation | Significant seizure reduction in uncontrolled human studies, but no significant change in controlled human trials (Walker 1938; Moruzzi and Magoun 1949; Cooper, Upton et al. 1982) |
| **Caudate** | Direct anterograde cortical stimulation | Significant seizure reduction in uncontrolled human studies (Sramka, Fritz et al. 1976; Chkhenkeli 1978) |
| **Posterior hypothalamus** | Direct anterograde cortical stimulation | Significant increase in seizure threshold in pentylenetetrazol (PTZ) rat model (Mirski and Fisher 1994) |
| **Anterior thalamic nucleus** | Direct anterograde cortical stimulation | One uncontrolled human study showing seizure reduction in 3 out of 5 patients (Cooper, Upton et al. 1980) |
| **Centromedian thalamic nucleus** | Direct anterograde cortical stimulation | Significant seizure reduction in uncontrolled human trials, but no significant change in controlled human trials (Velasco, Velasco et al. 1987) |
| **Subthalmic nucleus** | Nigral control of epilepsy system or antidromic cortical stimulation | Significant seizure reduction in uncontrolled human trials, but no controlled human trials performed (Vercueil, Benazzouz et al. 1998; Benabid, Minotti et al. 2002) |
| **Cortical stimulation** | Direct stimulation of epileptogenic focus | Brief bursts of pulse stimulation reported to terminate afterdischarges caused by cortical stimulation (Lesser, Kim et al. 1999; Luders, Najm et al. 2004) |
| **Hippocampal stimulation** | Direct stimulation of epileptogenic focus | Significant seizure reduction rats and in uncontrolled and controlled human studies (Velasco, Velasco et al. 2000; Albensi, Ata et al. 2004; Velasco, Velasco et al. 2007; Albensi, Toupin et al. 2008) |
| **Vagal nerve stimulation** | Direct anterograde cortical stimulation via activation of thalamic, brainstem, and limbic structures | Significant seizure reduction in rats and controlled human trials (Penry and Dean 1990; Woodbury and Woodbury 1990) |
| **Trigeminal nerve stimulation** | Direct anterograde cortical stimulation via desychronization of cortical and thalamic structures | Significant seizure reduction in rats, but no human studies to date (Fanselow, Reid et al. 2000) |
| **White matter tract stimulation** | Direct anterograde and retrograde stimulation of epileptogenic focus | Significant seizure reduction in rats, but no human studies to date (Luders, Najm et al. 2004) |

*Modified from, Luders et al., (Luders, Najm et al. 2004)

Table 1. Summary of Electrical Stimulation Studies in Epilepsy in Humans and Animal Models*

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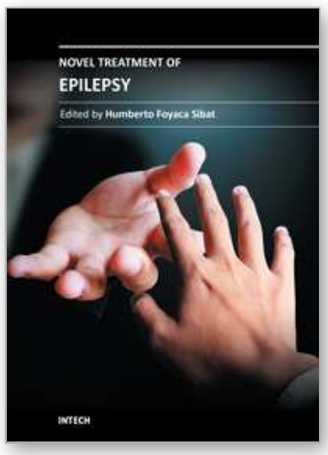


**Novel Treatment of Epilepsy**

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Epilepsy continues to be a major health problem throughout the planet, affecting millions of people, mainly in developing countries where parasitic zoonoses are more common and cysticercosis, as a leading cause, is endemic. There is epidemiological evidence for an increasing prevalence of epilepsy throughout the world, and evidence of increasing morbidity and mortality in many countries as a consequence of higher incidence of infectious diseases, head injury and stroke. We decided to edit this book because we identified another way to approach this problem, covering aspects of the treatment of epilepsy based on the most recent technological results â€œin vitroâ€ from developed countries, and the basic treatment of epilepsy at the primary care level in rural areas of South Africa. Therefore, apart from the classic issues that cannot be missing in any book about epilepsy, we introduced novel aspects related with epilepsy and neurocysticercosis, as a leading cause of epilepsy in developing countries. Many experts from the field of epilepsy worked hard on this publication to provide valuable updated information about the treatment of epilepsy and other related problems.

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