

Neuromodulatory Treatment of Medically Refractory Epilepsy

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1. Introduction

Epilepsy is a common chronic neurologic disorder affecting 0.5 to 1 percent of the population. (Hauser, 1993 4131) More than one-third of all epilepsy patients have incompletely controlled seizures or debilitating medication side effects in spite of optimal medical management. (Kwan et al. 2000; Sillanpaa et al. 2006; Sander et al. 1993) Medically refractory epilepsy is associated with excess injury and mortality, psychosocial dysfunction, and significant cognitive impairment. (Brodie et al. 1996) Treatment options for these patients include new anti-epileptic drugs (AEDs), which may lead to seizure freedom in 7 percent of patients (Fisher et al. 1993) and resective surgery which is associated with long-term seizure freedom in 60-80% of patients.(Engel et al. 2003 ;Lee et al. 2005) Surgery for patients whose epilepsy has proven refractory to AEDs provides a high likelihood of reduction in seizure frequency, is generally safe, and is recommended for selected patients with refractory partial seizures. In spite of improvements in surgical technique, approximately 4 percent of patients will suffer death or permanent neurologic disability (A global survey on epilepsy surgery, 1980-1990: a report by the Commission on Neurosurgery of Epilepsy, the International League Against Epilepsy 1997). Moreover, more than one-third of patients will not be candidates for surgical resection (Kwan et al. 2000). For patients who are not candidates for resective surgery, there are limited options. Neuromodulatory treatment, which consists of administering electrical pulses to neural tissue to modulate its activity leading to a beneficial effect, may be an option for these patients. The interest in neuromodulation for neurological disorders is driven by a desire to discover less invasive surgical treatments, as well as new treatments for patients whose medical conditions remain refractory to existing modalities. Vagal nerve stimulation (VNS) is one example of neuromodulation that was developed in the 1980s, and which is now routinely available. (Ben-Menachem et al. 2002) VNS, as an adjunct to medical management, may yield up to a 50 percent reduction in seizure frequency (A randomized controlled trial of chronic vagus nerve stimulation for treatment of medically intractable seizures. The Vagus Nerve Stimulation Study Group. 1995) although most of these patients will not be seizure-free. Deep brain stimulation (DBS) is another example of neuromodulation. Given the significant experience and success of DBS for movement disorders (Krack et al. 2003) combined with its reversibility, programmability, and low risk of morbidity, there has been

a resurgence of interest in using DBS devices for treating medically refractory epilepsy. Responsive neurostimulation is a technology that detects seizure activity at a previously defined focus and applies an electrical stimulus to the site of seizure onset to terminate the seizure. Transcranial magnetic stimulation (TMS) is a nearly 25-year-old technology initially introduced as a means to noninvasively investigate corticospinal circuits. Currently, TMS is used primarily in clinical neurophysiology. Importantly, TMS can be used to evaluate and manipulate excitatory and inhibitory intracortical circuits with post-stimulatory effect, allowing for a developing use in epileptic neuromodulation.

In summary, resective epilepsy surgery is not an ideal option for all patients with medically refractory epilepsy. It is an invasive, irreversible procedure which will not lead to a cure in all patients. It is associated with only modest success in patients with a normal MRI or a diffuse ictal onset zone. It has a significant risk of neurological or neuropsychological decline postoperatively. These factors in combination drive the search for alternative treatment options such as neuromodulation.

2. Vagal nerve stimulation

The vagal nerve has a complex anatomical arrangement which projects to the autonomic and reticular structures and well as limbic and thalamic neurons. Stimulation of the vagus nerve and its bilateral multisynaptic targets has become a common technology for the treatment of epilepsy. To date, over 50,000 patients have been treated with the technology, and current reports indicate an approximate 50% efficacy in seizure reduction, rivaling the efficacy of antiepileptic treatment, and often decreasing dependence on them (Labar et al. 2002). Efficacy has also been shown to increase over time (Vonck et al. 1999). The low side effect profile of vagal nerve stimulation (VNS) has also proven to be advantageous for users. Reported side effects mainly include hoarseness, paresthesias, shortness of breath, headache, and coughing (Morris et al. 1999). These effects are typically stimulation-related and resolve over time. (Boon et al. 1999) The mechanism of efficacy remains unknown, though certain structures within the brain appear to be affected by VNS. As evidenced by studies using positron-emission technology (PET), the thalamus is consistently affected by VNS stimulation, and bloodflow to the cerebellum and cerebral structures is consistently altered (Ko et al. 1996; Henry et al. 1999; Henry et al. 1998; Ben-Menachem et al. 2002). Thalamic involvement has also been supported through SPECT (Van et al. 2000; Vonck et al. 2000) and functional MRI.(Liu et al. 2003; Narayanan et al. 2002) analysis.

2.1 Animal studies

Studies of VNS have been reported from multiple vertebrate models including rodents (McLachlan et al. 1993), canines(Zabara et al. 1992) and lower primates. (Lockard et al. 1990) In the rodent penicillin/pentylentetrazol model, interictal spike frequency was reduced by 33%(McLachlan et al. 1993) the effect of which was later found to be greatest in continuous stimulation and reduced in a time-dependent fashion after stimulation. (Takaya et al. 1996) Later tests have shown that cortical excitability in rats can be modulated through VNS.(De et al. 2010) Canine strychnine and pentylentetrazol models show similar efficacy with lasting reduction in motor seizures and tremors. (Zabara et al. 1992) In the aluminagel monkey model, seizures were eliminated in half of test animals during stimulation periods with some persistence into post-stimulation periods. (Lockard et al. 1990)

2.2 Clinical studies

Clinical trials began in 1988 with the first open trial; preliminary results showed that such a therapy was potentially efficacious and safe with only transient side effects. (Penry et al. 1990) This was followed by a series of clinical trials from 1988 through 1995 which included two double-blind, randomized, controlled studies. (Handforth et al. 1998) Results indicated seizure reduction at both low and high stimulation paradigms, with significantly greater reduction in the high-stimulation group (Handforth et al. 1998) and overall efficacy showed a mean seizure reduction of approximately 35-45%. (Morris et al. 1999) Safety of the therapy was also established in this series of trials, with few patients discontinued secondary to adverse events. (Handforth et al. 1998) Vagal innervation of the larynx produced typical side effects including cough, dyspnea, and local paresthesia, though distal effects on the vagus were not appreciated. (Handforth, et al. 1998) The findings of these trials led to the widespread use of VNS therapy for complex partial and secondary generalized seizures in patients over 12 years of age. (Saillet et al. 2009) Since that time, data from pediatric studies have shown similar outcomes in younger patients. (Wheless et al. 2002)

In 2005, PuLsE: an open, prospective, randomized, parallel group study directly comparing best medical practice with and without adjunctive VNS Therapy was initiated (<http://clinicaltrials.gov/ct2/show/NCT01281280>). Long-term data were collected on both health outcomes and seizure frequency to determine if a possible significant clinical benefit in health outcomes over time of best medical practice with or without adjunctive VNS Therapy in patients with drug-resistant epilepsy with partial-onset seizures. Due to lower than anticipated enrollment, this study was discontinued in July 2008. The study was inconclusive due to inability to meet the primary objective with appropriate statistical power. However, due to a relatively large number of participants (n=121) randomized in the original PuLsE study, industry decided to implement an observational long-term follow-up of the participants enrolled in the original PuLsE study. This post-market study is designed to identify clinically and statistically significant predictors of response in patients with drug-resistant epilepsy with partial-onset seizures treated with best medical practice with or without adjunctive VNS Therapy. This is a 5-year study set to open in 2011 (<http://clinicaltrials.gov/ct2/show/NCT01281280>).

3. Transcranial magnetic stimulation

Transcranial magnetic stimulation (TMS) of cortical tissues was initially reported by Barker and colleagues and quickly found acceptance as a research vehicle for neurophysiologists. (Barker et al. 1985) TMS was first applied to the study of the motor system (Barker et al. 1985) and this use has since expanded to include investigations in psychiatric conditions (Pascual-Leone et al. 1996), migraine headache (Lipton et al. 2010) and other neurologic conditions. Importantly, it has also become a viable option for the treatment of drug resistant epilepsy. TMS exerts its effects through repetitive noninvasive stimulation in which a pulsed magnetic field creates current flow in the brain which can temporarily excite or inhibit target areas. (Hallett et al. 2000)

3.1 Animal studies

The basis of TMS as a therapeutic intervention in epilepsy is derived from the lasting effects that from the application of a train of transcranial stimuli. Theoretically, the lasting effects of

TMS can be used to modulate activity in focal areas of cortex.(Fregni et al. 2007) The TMS-induced effect depends on the nature of the stimulation; that is, the frequency, the timing, the focus, and the intensity of the repetitive stimulation. (Kimiskidis et al. 2010) While some paradigms have been studied using animal models, the numbers of basic studies particular to epilepsy are somewhat limited.

Early study within the mouse hippocampal-entorhinal cortex slice model indicated that repetitive direct (i.e., non-transcranial) stimulation at 1 Hz can depress the generation of ictal activity in a 4-aminopyridine model(Barbarosie et al. 1997), which later was shown to have a frequency-dependent effect.(D'Arcangelo, et al. 2005) This frequency dependence has been replicated in TMS. Low-frequency TMS stimulation shows the tendency to lower seizure activity. One study found that in rats, 1000 pulses of low-frequency TMS (0.5 Hz) reduced susceptibility to the induction of status epilepticus and also to increase the latency to onset of pentylenetetrazol-induced seizures.(Akamatsu et al. 2005) A later study indicated that in rats genetically modified as models of absence seizures, TMS could be used at 0.5 Hz to reduce spike wave discharge for a short, albeit statistically insignificant manner with maximal effect at 30 minutes.(Godlevsky et al. 2006) A more recent study suggests that TMS can suppress kainate-induced seizures in rats at frequencies of 0.5 and 0.75Hz though not at 0.25 Hz, demonstrating a frequency dependence on seizure control.(Rotenberg et al. 2008)

On the other hand, higher frequency stimulation has been shown to have confounding effects. Using male Wistar rats, it was shown that in the pentylenetetrazole model of clonic seizures, chronic high-frequency stimulation (50Hz) may induce kindling of seizure activity, though this effect was not appreciated with acute-only stimulation.(Jennum et al. 1996) Later work indicated that an acute high-frequency (20 Hz) TMS train significantly increased the threshold for induction of epileptic after-discharges in amygdala-kindled rats, with effects lasting at least 2 weeks, though it was not directly compared with chronic stimulation.(Ebert et al. 1999) High frequency stimulation has been shown therefore to potentially have both protective and inductive effects dependent on the chronicity of treatment and potentially other, unexplored, factors.

3.2 Clinical studies

Similar results have been identified in human studies. High frequency TMS (>5 Hz) has been shown to enhance cortical excitability at high intensities.(Berardelli et al. 1998) Alternatively, low-frequency TMS (i.e. ≤ 1 Hz), has been shown to reduce cortical excitability, potentially secondary to an increase in the refractory neuronal period(Cincotta et al. 2003) as well as decreased strength of neuronal signaling.(Muellbacher et al. 2000)

As detailed by Kimiskidis (Kimiskidis 2010), the clinical effects are theoretically similar to long term potentiation (LTP) and long-term depression (LTD) elicited by high- and low-frequency electrical stimulation, respectively. It is therefore possible that TMS at lower frequencies may exert its effect through the initiation of LTD, while at higher frequencies, the proconvulsant effect may be initiated through the induction of an LTP-type effect.(Ziemann U. et al. 2005)

Multiple investigations into the effect of low-frequency TMS on multiple seizure types have been reported utilizing variable targeting, frequency, intensities, and train parameters. One of the first open-label pilot trials of this technology demonstrated at least a six-week reduction in the frequency of epileptic events using a frequency of 0.33 Hz (Tergau et al.

1999) Theodore et al. reported a statistically insignificant and short-lived trend towards seizure reduction in a randomized trial of 12 focal epilepsy patients at a frequency of 1 Hz.(Theodore et al. 2002) A later trial involving 17 patients utilizing both frequencies demonstrated seizure reduction at the lower frequency of 0.33 Hz only.(Tergau et al. 2003) TMS applied at a frequency of 0.5 Hz in a single session was associated with an approximate 42% reduction of epileptiform discharges lasting at least 30 days in a population of cortical dysplasia patients in an open-label study.(Fregni et al. 2005) A larger, randomized follow-up trial using a frequency of 1 Hz showed a reduction of seizure activity when compared with the sham group, with effects lasting at least 60 days.(Fregni et al. 2006) In another extratemporal focal epilepsy series, TMS applied at a frequency of 0.9 Hz, demonstrated a favorable though statistically insignificant trend towards seizure reduction.(Kinoshita et al. 2005) Larger randomized trials have indicated encouraging though statistically insignificant decreases in epileptic activity. In a series of 35 patients with focal, nonfocal and multifocal epilepsy, stimulation at vertex and temporal targets at a frequency of 0.5 Hz reduced interictal spikes by greater than 50%, though seizure reduction was non-significant. It should be noted that the trend was toward reduction, and target of TMS was non-influential on the outcome.(Joo et al. 2007) Cantello et al.(Cantello et al. 2007) similarly found an appreciable decrease in interictal epileptiform abnormalities in approximately one-third of a series of 43 patients with mostly focal epilepsy in a randomized double-blind study, though the clinical antiepileptic activity was insignificant

As can be appreciated from these findings, the antiepileptic effects of TMS show somewhat ambiguous results even when accounting for different stimulation paradigms and locations. The efficacy of this technology will therefore need careful scrutiny from the perspective of larger randomized trials and carefully conducted meta-analyses accounting for differences in localization of epilepsy, stimulation paradigms, frequency, target and repetition and potential placebo effects.(Bae et al. 2011) The safety of this therapy may also be of concern, as there have been reports of seizures related to therapy.(Tergau et al. 1999; Bae et al. 2007; Rotenberg et al. 2009) Generally, however, the therapy is considered safe, with common adverse effects including headache (<10%) and mild discomfort.(Bae et al. 2007)

4. Deep brain stimulation (open-loop)

DBS lead implantation within the anterior nucleus of the thalamus (ANT), as well as other central nervous system (CNS) targets - including the caudate nucleus, centromedian nucleus of the thalamus, cerebellum, hippocampus, and subthalamic nucleus - results in seizure reduction in selected patients.(Vercueil et al. 1998; Shandra et al. 1990; Mirski et al. 1986; Bragin et al. 2002) In all of these studies, the stimulation was delivered in an open-loop fashion, that is, in a pre-defined manner, independent of the momentary physiological activity of the brain. The exact mechanism of action of DBS in reducing seizure activity is unknown. It is known that stereotactic lesions of the ANT in humans can result in reduction in seizure frequency. (Mullan et al. 1967) Some evidence suggests that DBS may interfere with synchronized oscillations by neurotransmitter release.(Lee et al. 2005) Other evidence suggests that the most likely mechanism may involve stimulation-induced modulation of pathologic neural networks.(McIntyre et al. 2004) High-frequency DBS appears to reproduce the clinical effect of ablative procedures.(Benabid et al. 1987) Moreover, at high frequencies, DBS may abolish cortical epileptiform activity.(Lado et al. 2003) A microthalamotomy effect has been postulated based on the observation that some patients

obtain reduction in seizure frequency prior to activation of the pulse generator. (Lim et al. 2007 ; Andrade et al. 2006)

Although the precise mechanism by which DBS reduces seizure activity is unclear, inhibition of neurons immediately adjacent to the area of applied current is likely involved.

A "reversible functional lesion" may be generated in structures integral to initiating or sustaining epileptic activity. (Boon et al. 2007) The applied current may inhibit neurons with a pathologically lowered threshold of activation. Alternatively, DBS may act on neuronal network projections to nearby or remote CNS structures originating from the area of stimulation. This might take place through either activation of inhibitory projections or through the inhibition of excitatory projections.

DBS for movement disorders has met with widespread success (Nguyen et al. 2000; Pollak et al. 2002; Volkmann et al. 2004) and is increasingly being investigated for new indications such as chronic pain, obsessive-compulsive disorders, and even headache. (Gybels et al. 1993; Leone et al. 2005; Leone et al. 2003) While DBS of targets such as the thalamus, cerebellum, and locus ceruleus was performed in the past in patients with psychiatric disorders or spasticity who also had seizures, technical limitations prevented it from becoming an appropriate treatment option for patients with epilepsy alone. (Cooper et al. 1976; Wright et al. 1984; Upton et al. 1985; Feinstein et al. 1989) A renewed interest in DBS for epilepsy has arisen from success with the technique in movement disorders, along with technological improvements in the equipment. Multiple epilepsy centers throughout the world have performed trials over the years using DBS for epilepsy, targeting a variety of CNS structures. (Fisher et al. 1992; Velasco et al. 1995; Chkhenkeli et al. 1997; Chabardes et al. 2002; Hodaie et al. 2002; Velasco et al. 2005) These trials can be summarized based on two different strategies.

One strategy is to target CNS structures believed to have a "gating" role in the epileptogenic network, such as the subthalamic nucleus or thalamus. (Iadarola et al. 1982) The other strategy is to target the ictal onset zone with the theory that stimulation may lead to interference with seizure initiation. The latter strategy might ideally be used in patients with mesial temporal lobe (MTL) epilepsy given the success in reducing seizures in patients after anterior temporal lobectomy. (Engel et al. 2003) MTL epilepsy is the most common form of medically refractory partial epilepsy. These patients have a long-term freedom from seizure rate of 60 to 75 percent after undergoing temporal lobectomy. In spite of undergoing satisfactory preoperative Wada testing, however, many of these patients will demonstrate a verbal memory deficit on postoperative neuropsychological evaluation. (Helmstaedter et al. 2003; Gleissner et al. 2004) Given that some of these patients must undergo implantation of electrodes prior to considering resection, they may be ideal candidates for using DBS with the same electrodes used for diagnostic purposes.

4.1 Animal studies at various anatomic sites

Numerous animal models have been used to elucidate DBS mechanism of action and its potential usefulness in the treatment of epilepsy. (Ziai et al. 2005; Wyckhuys et al. 2007; Usui et al. 2005; Shi et al. 2006; Nishida et al. 2007; Lian et al. 2003; Jensen et al. 2007) Animal epilepsy models have utilized pentylenetetrazol (PTZ), kainic acid (KA), bicuculline (BIC), picrotoxin, and kindling to induce seizures. (Ziai et al. 2005; Usui et al. 2005; Shi et al. 2006; Nishida et al. 2007; Lian et al. 2003; Jensen et al. 2007; Mirski et al. 1986) Sinusoidal alternating current (AC) versus direct current (DC) stimulation protocols, synaptic versus

non-synaptic inhibition, regional alterations in neurochemistry, and differing anatomic targets are among many variables investigated in these models. (Ziai et al. 2005; Nishida et al. 2007; Lian et al. 2003; Jensen et al. 2007)

4.1.1 Cerebellum

Cooke and Snider (Cooke et al. 1955) demonstrated that cerebellar stimulation (CS) can modify or abruptly terminate seizure activity in various cerebral areas. Iwata and Snider (IWATA et al. 1959) observed that CS could terminate hippocampal seizures and prolonged afterdischarges (AD) that had been induced by electrical stimulation. In 1962, Dow et al. (Dow et al. 1962) showed that CS could alter electroencephalogram (EEG) activity and reduce frontal lobe seizures in a model of chronic epilepsy in awake unanesthetized rats. Fanardjian and Donhoffer (Fanardjian & Donhoffer 1964) found CS induced slow waves in the normal hippocampus while activation-like patterns appeared simultaneously in the cerebellum. In 1980, Laxer et al. (Laxer et al. 1980) found inconsistent results when reviewing studies from 22 groups using CS with a wide range of stimulation parameters. They were nonetheless able to draw two conclusions: (a) stimulation of the vermis and superomedial surface is more effective than stimulation of the lateral hemisphere, and (b) CS is most effective in epilepsy of the limbic system, and least effective in models of focal epilepsy of the sensorimotor cortex.

4.1.2 Hippocampus

Lian et al. (Lian et al. 2003) tested the effects of DC stimulation and low-duty cycle AC stimulation (which more closely approximates that used clinically) in a hippocampal slice epilepsy model. They demonstrated that continuous sinusoidal, 50% duty-cycle sinusoidal, and 1.68% duty-cycle pulsed stimulation (120 μ sec, 140Hz) all suppressed low-Ca²⁺ epileptiform activity. Continuous sinusoidal stimulation was also found to completely suppress picrotoxin-induced epileptiform activity. AC stimulation resulted in an increase in extracellular potassium concentration and neuronal depolarization blockade, and was not found to be slice orientation-selective. DC stimulation by contrast, suppressed epileptiform activity only in the region surrounding the electrode, and did so by membrane hyperpolarization.

Jensen and Durand (Jensen & Durand 2007) recently demonstrated that in vitro sinusoidal high frequency stimulation of rat hippocampal slices suppresses axonal conduction. Stimulation was found to suppress the alvear compound action potential as well as the antidromic evoked potential. The stimulation frequency at which maximal suppression occurred was between 50 and 200 Hz, similar to that observed in most clinical DBS studies. The degree of suppression of axonal conduction correlated with a rise in extracellular potassium demonstrating that stimulation may block axonal activity through non-synaptic mechanisms.

4.1.3 STN and SNr

DBS of the substantia nigra pars reticulata (SNr) completely blocked amygdala-kindled seizures in 10 of 23 (43.5%) rats studied by Shi (Shi 2006). Microwire electrodes were implanted into the SNr and amygdala of adult male rats. Seizures were produced by daily amygdala kindling, and DBS was delivered to the SNr bilaterally 1 sec after kindling stopped. When the same amygdala kindling procedure was performed 24h later without

DBS, the kindling failed to elicit any seizures in 6 of the 10 rats. In 3 animals, only mild seizures appeared following amygdala kindling. Only 1 of the 10 responders exhibited stage 5-kindled seizures 24h after DBS was discontinued. In 9 of the 10 responders, the period of seizure suppression or reduction lasted for up to 4 days. The authors concluded that highly plastic neural networks may be involved in amygdala-kindled seizures and that DBS may exert long lasting effects on these networks.

In contrast, when Usui et al. (Usui et al. 2005) tested SNr DBS in rats with KA induced seizures they found no treatment effect. They compared one group of rats with a unilateral SNr electrode to a second group with a unilateral subthalamic nucleus (STN) electrode. A control group received no electrodes. KA was systemically administered to all three groups to induce limbic seizures, and DBS of the STN or SNr was begun immediately afterward. EEG changes and the magnitude of clinical seizures were then evaluated. They demonstrated that unilateral STN stimulation significantly reduced the duration of generalized seizures on EEG. Interestingly, the duration of focal seizures on EEG was prolonged by STN DBS, a result felt possibly due to the suppression of secondary generalization. In addition, STN DBS reduced the severity of clinical seizures. The group receiving SNr DBS demonstrated no significant effect when compared to the controls. They concluded that unilateral STN DBS suppresses secondary generalization of limbic seizures. The failure of SNr DBS to reduce secondary generalization was felt to imply that, while nigral influence on seizure propagation may be important, other antiepileptic mechanisms such as antidromic stimulation of the corticosubthalamic pathway may also be involved.

4.1.4 Anterior nucleus of the thalamus

The hypothesis that the ANT participates in the propagation of some forms of seizures is supported by experimental animal studies. Low frequency (8Hz) stimulation of the ANT has been found to be epileptogenic (Lado et al. 2003). Seizures can be induced in guinea pigs by microinjection of KA, BIC, or PTZ into the ANT. (Mirski et al. 1986) Hamani et al. (Hamani et al. 2004) discovered that bilateral, high frequency ANT DBS delays the onset of status epilepticus (SE) after exposure to pilocarpine. In their study, adult Wistar rats underwent unilateral or bilateral ANT lesioning, or unilateral or bilateral ANT DBS electrode placement. The control group received bilateral ANT electrodes but no stimulation. Seven days later, the animals were given pilocarpine, after which EEG recordings and ictal behavior were evaluated. In the control group, 67% of the animals developed SE with a latency of 15.3 +/- 8.8 minutes after pilocarpine administration. Neither unilateral ANT lesions nor unilateral ANT DBS significantly reduced the likelihood or latency of SE. Bilateral ANT DBS did not prevent SE (observed in 56% of the animals), but did significantly prolong the latency to 48.4 +/- 17.7 min ($p = 0.02$). Interestingly, no animals with bilateral ANT lesions developed SE with pilocarpine.

4.2 DBS clinical studies at various anatomic sites

4.2.1 Cerebellum

Cooper et al. (Cooper et al. 1976) were the first to report on CS for epilepsy, and observed that 10 of the 15 patients in the trial experienced a reduction in seizure frequency of $\geq 50\%$ when followed up to 3 years. Stimulation of the anterior lobe appeared to be more effective than that of the posterior lobe. Cerebellar biopsies, obtained in five patients at the time of lead placement, revealed a reduction in the molecular layer, decreased or absent Purkinje

cells, and decreased stellate cells. One patient, who failed to respond to stimulation, died as a result of a seizure 17 months after implantation. Davis and Emmonds (Davis, 1992 4120) subsequently discovered that 23 of 27 evaluable patients who underwent long-term (average follow-up 14.3 years) CS had an overall reduction in seizure frequency. Interestingly, 12 of the patients had a non-functioning stimulator at the time of the report and yet 5 were found to be seizure-free, while 7 had experienced a reduction in seizure frequency.

Wright et al. (Wright et al. 1984) examined twelve patients with severe, intractable epilepsy who underwent CS under double-blind conditions for six months. The trial was divided into three phases, each lasting two months. Patients received two months of continuous stimulation (alternating from one cerebellar hemisphere to the other every minute), two months of contingent stimulation (during which both hemispheres were stimulated only while a button was depressed by the patient or family member), and two months of no stimulation. The sequence of phases was randomly assigned and the patients, family members, and evaluators were blinded to each epoch. No reduction in seizure frequency occurred that could be attributed to stimulation. However, most patients reported a reduction in the duration and severity of seizures although these were not measured during the study. Eleven of the patients considered that the trial had helped them and wished to continue "stimulation" at the conclusion of the trial.

Velasco et al. (Velasco et al. 2005), in a more recent double-blind trial with two years of follow-up in five patients undergoing CS, demonstrated improvement in seizure control. Beginning one month after implantation and for a period of 3 months, 3 patients were assigned randomly to receive stimulation while 2 others had their stimulators left OFF. After the fourth month, all patients were then ON stimulation for the next 6 months. During the 3-month double-blind phase, the two patients with stimulation OFF demonstrated no difference in mean seizure rate compared to baseline. During the same phase, the 3 patients with stimulation ON demonstrated a reduction in seizure rate to 33% of baseline. At the end of the subsequent 6 months, all five patients had a mean seizure rate of 41% (range 14-75%) of baseline. The improvement in generalized tonic-clonic seizures occurred earlier and to a greater degree than that for tonic seizures.

It is likely that CS results in the activation of Purkinje cells which exert inhibitory output on the deep cerebellar nuclei. CS likely reduces excitatory cerebellar output from these nuclei to the thalamus, leading to a reduction in output from excitatory thalamocortical projections, and thus inhibition of cortical activity. (Molnar et al. 2004)

4.2.2 Hippocampus

Evidence strongly suggests that the hippocampus is involved in the initiation and propagation of temporal lobe seizures. (Swanson et al. 1995; Sperling et al. 1992) Velasco et al. (Velasco et al. 2000) demonstrated that hippocampal stimulation using electrode grids or depth electrodes significantly reduced interictal spikes and abolished complex partial and secondarily generalized tonic-clonic seizures in 7 of 10 patients with intractable temporal lobe epilepsy. The same group, in a subsequent study, observed that chronic hippocampal stimulation in three patients reduced seizure activity without affecting short-term memory. (Velasco et al. 2001)

Vonck et al. (Vonck et al. 2002) conducted an open label trial involving three patients with complex partial seizures who underwent DBS of the amygdalohippocampal region. Two DBS electrodes were implanted in each hemisphere through two occipital burr holes. This

procedure was performed on the same day as placement of subdural grids and strips. The most anterior electrode on each side was placed in the amygdala. The second electrode was placed more posteriorly in the anterior part of the hippocampus on each side. AEDs were gradually tapered until seizures were observed. During a trial phase, stimulation was applied to both the amygdalar and hippocampal electrodes. The frequency was set to 130Hz and pulse width to 450 μ sec. Seizure frequency during the chronic stimulation condition was then compared with the mean monthly seizure frequency recorded 6 months before DBS placement. At a mean follow-up of 5 months (range, 3-6 months), all three patients had a greater than 50% reduction in seizure frequency. In two of the patients, AEDs were tapered. No side effects of stimulation were noted by the patients.

4.2.3 Centromedian nucleus of the thalamus (CMT)

The CMT arises from the diencephalon and brain stem, projecting diffusely to the cerebral cortex as part of the ascending subcortical system. The CMT may play a role in the pathophysiology and propagation of seizures. (Velasco et al. 2000) DBS of the CMT may result in hyperpolarization and desynchronization of the ascending reticular and cortical neurons. (Velasco et al. 2000)

Fisher et al. (Fisher et al. 1992) implanted programmable stimulators into CMT bilaterally in 7 patients with intractable epilepsy to test feasibility and safety. Stimulation was ON or OFF in 3-month blocks, with a 3-month washout period in a double-blind, cross-over protocol. The stimulation was delivered as 90 μ sec pulses at 65 pulses/sec, 1 min. of each 5 min. for 2 hours/day. They noted a mean reduction of tonic-clonic seizure frequency of 30% with respect to baseline when the stimulator was ON compared to a decrease of 8% when the stimulator was OFF. Stimulation at low intensity produced no changes in the EEG, but high-intensity stimulation induced slow waves or 2-3 Hz spike-waves with ipsilateral frontal maximum. When the stimulator trains were continued for 24 hours/day, 3 of 6 patients reported at least a 50% decrease in seizure frequency. There were no side effects reported.

A recent trial of CMT DBS in 13 patients with Lennox-Gastaut Syndrome (LGS) revealed an overall seizure reduction rate of 80 percent, and significant gains in quality of life. (Velasco et al. 2006) LGS is one of the most severe forms of childhood epilepsy characterized by drug-resistant generalized seizures in conjunction with mental deterioration. The overall prognosis is very poor with 90% of patients being mentally retarded and 80% continuing seizures into adulthood. The 13 patients implanted in this study tolerated the procedure well, although two had to be explanted due to multiple repeated erosions through the skin. Three patients experienced no improvement in their ability scale score due to persistent seizures. Two patients became seizure-free during the 18 month follow-up, while 8 experienced progressive improvement (5 of the 8 became completely independent).

4.2.4 Subthalamic nucleus

The abundant experience of STN DBS for treating patients with Parkinson's disease makes STN a familiar and attractive target (Halpern et al. 2007). The substantia nigra pars reticulata (SNr) appears to be involved in propagation of seizures through GABAergic projections to the superior colliculus (Gale et al. 1986). It is recognized that STN outputs produce excitatory influence over the SNr system, and that electrical or pharmacologic inhibition of the STN in rats can result in seizure suppression. (Vercueil et al. 1998)

High frequency bilateral STN DBS in a child with cortical dysplasia and inoperable epilepsy resulted in an 83 percent improvement in seizure frequency at 30 months, reduction in seizure severity, and a recovery of motor function. (Benabid et al. 2001) In the same report, Benabid noted a 50% reduction in seizures in one patient with severe myoclonic epilepsy undergoing bilateral STN DBS.

Loddenkemper et al. (Loddenkemper et al. 2001) reported on five patients undergoing STN DBS implantation for pharmacologically intractable seizures. The patients underwent constant stimulation at a frequency of 100Hz, and stimulus duration of 60 μ sec. In 2 of the 5 patients, an 80% reduction of seizures was noted after 10 months and 60% reduction at 16 months. They hypothesized that the dorsal midbrain anticonvulsant zone in the superior colliculus is under inhibitory control of efferents from the SNr. In this model, inhibition of the STN is believed to reduce the inhibitory effect of the SNr on the dorsal midbrain anticonvulsant zone, thereby raising the seizure threshold.

Chabardes et al. (Chabardes et al. 2002), in an open label study of STN DBS, implanted 5 patients with medically intractable seizures who were considered unsuitable for resective surgery. A 67-80% reduction in seizure frequency was noted in 3 of the 5 patients. A fourth patient with severe myoclonic epilepsy (Dravet syndrome) had a less impressive reduction. The fifth patient, who showed no improvement with the treatment, suffered from an autosomal dominant form of frontal lobe epilepsy.

More recently, Handforth et al. (Handforth et al. 2006) reported their results in two patients with refractory partial onset seizures who were treated with bilateral STN DBS. In one patient, seizure frequency was reduced by one-third, and the patient's quality of life was improved as a result of milder, less harmful seizures. The other patient continued to have seizure-related injuries in spite of a 50% reduction in seizure frequency. To better understand the potential of STN DBS as a treatment for medically refractory epilepsy, more trials will be necessary.

4.2.5 Caudate nucleus

The caudate loop is a functional unit made up of the neocortex, thalamus, and head of the caudate nucleus (HCN) (Heuser et al. 1961). Chkhenkeli et al. (Chkhenkeli et al 2004) examined 57 patients with test stimulation of the HCN, 17 of whom went on to have implantation of a neurostimulator for therapeutic purposes. They discovered that short duration, high frequency (2-5s, 30-100Hz) stimulation of the dorsal and ventral HCN produced enhancement of epileptiform spike and/or sharp wave activity. By contrast, low frequency (4 to 8Hz) stimulation of similar duration reduced the frequency of sharp transients in the interictal epileptic activity and truncated epileptic discharges from the temporal neocortex. Overall, 14 of 17 patients experienced a reduction in seizure frequency. They postulated that activation of the head of the CN results in hyperpolarization of cortical neurons, and that stimulation-induced inhibition can theoretically suppress seizure activity.

4.2.6 Anterior nucleus of the thalamus (ANT)

Low frequency (8Hz) stimulation of the ANT has been found to be epileptogenic. (Lado et al. 2003) Seizures can be induced in guinea pigs by microinjection of the excitatory agents KA, BIC, or PTZ into the ANT. (Mirski et al. 1986) Placement of DBS electrodes bilaterally into ANT delays the onset of status epilepticus after exposure to pilocarpine. (Hamani et al. 2004) Given the absence of anticonvulsant effect noted in numerous studies, as well as the

proconvulsant effects noted in others, the efficacy of chronic ANT DBS for epilepsy in animal studies remains incompletely defined. (Hamani et al. 2004; Lado et al. 2006)

Upton et al. (Upton et al. 1987) treated six patients (five male, one female, mean age 23.7 years) with debilitating, medically refractory seizures by pulsed electrical stimulation of the ANT. In four of the six patients, statistically significant reduction in seizure frequency was obtained. In two of the six patients, they observed changes in regional cerebral glucose metabolism, serum levels of AEDs, and serum cortisol levels ON and OFF stimulation. They concluded that stimulation of the ANT produces not only clinical and electroencephalographic changes, but also changes in cerebral metabolic, endocrinologic and pharmacokinetic responses.

Recently, Osorio et al. (Osorio et al. 2007) reported on the safety and efficacy of high frequency ANT stimulation in patients with inoperable MTL epilepsy. Four patients underwent bilateral implantation of DBS leads in the ANT, followed six weeks later by generator implantation. The mean stimulation parameters were: 175 Hz, 4.1V, pulse width of 90 μ sec. The stimulation was intermittent with one minute ON and five minutes OFF. The efficacy of stimulation was evaluated by comparing seizure frequency during a 36-month treatment period to a 6-month baseline obtained prior to implantation. They noted a mean reduction in seizure frequency of 75.6% (range 53-92%). Quality of life indices improved in all four subjects, and there were no serious adverse events reported. They concluded that high frequency intermittent thalamic stimulation is safe and efficacious for inoperable MTL. Lee et al. (Lee et al. 2006) reported on six patients with medically refractory, surgically inoperable epilepsy who were implanted with DBS electrodes (three in ATN, three in STN). Seizure frequency and severity were observed and compared to baseline. The stimulators were turned ON one week after insertion of the electrodes. The patients undergoing implantation within ANT experienced a 75.4% reduction in seizure frequency, while those with STN electrodes had their seizure frequency reduced by 49.1%.

Long-term follow-up was reported by Lim et al. (Lim et al. 2007) in four patients who underwent bilateral DBS implantation within the ANT. Initial stimulation parameters were 90-110Hz, 4-5V, and 60-90 μ sec. For each patient, seizure frequency at baseline and after implantation was analyzed. An average reduction in seizure frequency of 67% (range 44-94%), was noted during the sham interval. Once the stimulators were turned ON, a 49% (range 35-76%) reduction in seizure frequency was noted over the subsequent follow-up period (mean 43.8 months, range 33-48 months). One patient inadvertently had the stimulator turned OFF from months 7-12, during which the seizure frequency increased compared to baseline. No significant difference in seizure frequency was noted between the cycling and continuous stimulation intervals. One patient was seizure-free on medication for 15 months after implantation. No permanent neurological morbidity was observed. While a reduction in seizure frequency was noted during this study, the authors could not demonstrate whether a lesioning effect, subsequent stimulation, or changes in AEDs had the greatest impact.

Hodaie et al. (Hodaie et al. 2002) implanted bilateral DBS electrodes in the ANT of five patients with medically refractory epilepsy who were not eligible for resective surgery. The stimulators were then turned ON 4 weeks after implantation. Stimulation parameters were: 100Hz, 10V, 90 μ sec pulse width, cycling one minute ON and five minutes OFF, alternating left and right sides. AEDs were unchanged for the duration of the study. For each of the patients, pre- and post-operative seizure rates were evaluated using a one-way analysis of variance (ANOVA; *F* test). The average follow-up time was 14.9 months (range 10.6-20.7

months). The seizure reduction rate ranged between 24 and 89% (mean 53.8%, $p < 0.05$). Two of the patients had $>75\%$ reduction in seizure frequency. They noted that merely inserting the electrodes resulted in reduced seizure frequency, and that turning the stimulator ON at 4 weeks yielded no additional reduction. After an interval of continuous stimulation ranging from 7-17 months, each of the patients had their stimulators turned OFF in a blinded fashion for 2 months. Seizure rates were then compared between these ON and OFF intervals. No significant difference in the rate of seizure reduction was observed between the two intervals. The only adverse surgical event was erosion of the skin over the DBS site, requiring wound revision in one patient.

Kerrigan et al. (Kerrigan et al. 2004) conducted an open-label pilot study in 5 patients to investigate the safety and tolerability of bilateral stimulation of the ANT and to investigate the range of appropriate stimulation parameters. Patients enrolled in the study had medically intractable partial seizures and were not candidates for surgical resection. Four of the five patients also had secondarily generalized seizures. After completing implantation, long-term ANT stimulation was then performed intermittently, with the stimulator on each side programmed to produce 1 min of stimulation every 10 min. Stimulation on each side was offset by 5 min. Stimulation parameters were: frequency of 100 Hz, pulse width of 90 μ sec and intensity of 1-10V. The voltage was incrementally increased over a period of 12-30 weeks, depending on the clinical response of each patient. Seizure counts were monitored through the use of daily diaries and were compared to baseline. AEDs were unchanged during the first 3 months of stimulation, but were adjusted thereafter. The baseline average monthly seizure frequency across all five patients was 46.8 \pm 26.4 (mean \pm SD). During the 12-month treatment period of high-frequency stimulation, the average monthly seizure frequency for the group dropped to 25.0 \pm 11.5 (mean \pm SD), although this was not a statistically significant difference. Only one subject had a statistically significant ($p < 0.05$) reduction in overall seizure frequency. However, 4 of the 5 patients demonstrated reduction in the incidence of injurious seizures to $<50\%$ of their baseline incidence.

Andrade et al. (Andrade et al. 2006) reported the long-term follow-up of 6 patients who underwent bilateral ANT DBS for epilepsy. Three patients had generalized epilepsy with tonic-clonic seizures while the other three had multi-focal/partial epilepsy with secondarily generalized seizures. Programming was initiated 1 month after insertion of electrodes. AEDs were not changed for the two years of follow-up. Stimulation parameters were: frequency of 100-185Hz, intensity of 1-10V, and pulse duration of 90-120 μ sec. The first five patients implanted underwent a 2-month, single-blind period of sham stimulation, during which the generator was OFF. Implantation of the DBS electrodes resulted in statistically significant reduction in seizure frequency in all six patients. Five of the patients had a 50% or greater reduction, although two of the patients received no benefit until years 5 and 6, and only after changes in AEDs. Changes made to stimulation parameters could not be correlated with success in seizure control. Moreover, during the single-blind, 2-month period of stimulation OFF, there was no difference in seizure rates. The only adverse event was a 4-day period of lethargy in one of the patients. Otherwise, even at maximum voltage, the patients were not able to tell if their stimulators were ON or OFF.

5. Responsive neurostimulation (closed-loop)

In contrast to open-loop stimulation, contingent or closed-loop stimulation is designed to suppress epileptiform activity by stimulating a target directly in response to abnormal EEG

activity. This form of closed-loop, responsive brain stimulation, is currently available in a clinical setting in the form of the RNS system by Neuropace (Mountain View, CA). It is currently being evaluated in a multi-center, double-blinded, randomized trial to assess the safety and efficacy.

5.1 Animal studies

In 1983, Psatta first examined the effects of low-frequency (5 hz) feedback caudate nucleus stimulation on the interictal spiking activity of epileptic foci detected in adult cats. (Psatta et al. 1983) Spike depression was found to occur immediately after the onset of feedback stimulation and became stable after 3-4 days. Similar effects were not observed when the caudate nucleus was stimulated randomly, nor as a result of contingent stimulation of other subcortical structures. He hypothesized the existence of a recurrent inhibitor caudate-cortical loop as the anatomic mechanism for the normalization of cortical excitability.

In 1991 Nakagawa and Durand presented the effects of applied current on spontaneous epileptiform activity in the CA1 region of the rat hippocampus. (Nakagawa & Durand 1991) A computer-controlled system was used to detect spontaneous, abnormal EEG activity in a slice model using elevated potassium artificial CSF. The system, in response to the abnormal EEG activity, delivered electrical currents (average 12.5 microA) to the stratum pyramidale which suppressed interictal bursts in 90% of the slices. Using intracellular recordings, they determined that the currents induced hyperpolarization of the somatic membrane, thereby inhibiting neuronal firing.

In 1998, Kayyali and Durand reported their results from recordings of the CA1 region in a rat hippocampal slice model in which low-Ca²⁺ artificial CSF was used to induce spontaneous epileptiform events. (Kayyali, & Durand 1991) Activity was recorded with a glass pipette electrode and voltage threshold detector, after which current (average 3.8 microA) was injected in the stratum pyramidale via a tungsten electrode placed 150 microns from the recording site. They observed a complete suppression of epileptiform events by subthreshold anodic current pulses that in some cases were shorter in duration than the event itself.

5.2 Clinical studies

The first clinical experiments demonstrating the application of responsive stimulation were trials conducted on patients undergoing invasive monitoring and stimulation mapping to localize seizure onset prior to a planned epilepsy surgery. In stimulation mapping, electrical pulses are applied at increasing amplitudes until a clinical alteration or after-discharge is evoked. Lesser et al. reported that short duration (0.3-2 s) pulses were more effective than longer duration (4-5 s for typical stimulation mapping) pulses in reducing after-discharges. (Lesser et al. 1999) Specifically, they noted that for a every 1-s increase in stimulation duration, there was a 40% reduction in eliminating after-discharges. In a related report, Motamedi et al. (Motamedi et al. 2002) demonstrated that stimulation pulses were more effective in eliminating after-discharges if applied early.

Although after-discharges are similar in morphology to spontaneous discharges and can evolve into seizures, they are not the same as spontaneous epileptiform activity. Delivering a stimulation in response to spontaneous epileptiform activity requires an integrated system that analyzes the EEG in real-time and automatically produces pulses in response to a detected event. Peters et al. described such a system in 2001 consisting of a combination of

custom-written software and commercially available hardware and software.(Peters et al. 2001) The custom-written software included a unique detection algorithm to detect events early and nearly in real time.(Osorio et al. 1998) Using this system, the authors were able to detect electrographic seizure onset with a latency of approximately 4-12 seconds, noting that in most of their patients the clinical onset was multiple tens of seconds later. (Osorio et al. 2002; Osorio et al. 2005) This system was evaluated in a trial of eight patients. In four of these patients, the stimulation was automatically delivered to the ANT, while the other four had responsive stimulation administered into the epileptogenic zone. The authors observed three of four responders (>50% seizure reduction) in the group with direct stimulation of the epileptogenic zone, and two of four responders in the patients receiving stimulation to the ANT.

Kossoff et al. reported on four patients treated with responsive stimulation while implanted with electrodes for purposes of localization.(Kossoff et al. 2004) This open trial evaluated clinical and EEG responses to stimulation from an external device that detected electrographic seizures and delivered preprogrammed stimulation. In all four patients responsive stimulation appeared to be safe and well tolerated, although two patients experienced sensations in the face and tongue. While the study was designed to evaluate efficacy, stimulation appeared to reduce the number of clinical and electrographic seizures.

5.3 The neuropace RNS system

Success with external responsive neurostimulators in the prior animal and clinical studies led to the development of the first implantable system for epilepsy, the RNS system by Neuropace. This device is capable of performing real-time seizure detection and applying responsive electrical stimulation to abort seizures. The device is made up of intracranial depth and strip leads and an implanted neurostimulator. The system is controlled by a microprocessor, powered by a battery, and continuously monitors electrographic activity from the leads, applying preprogrammed stimulation in response to detected events. Because the system has two leads (each with four electrode contacts) , it can monitor and deliver responsive neurostimulation to two different epileptogenic regions simultaneously. In addition to the implantable hardware, the system includes a patient data transmitter, a physician programming device, and a telemetry wand. The transmitter allows the patient to upload data between visits to allow remote monitoring. The programmer is utilized by the physician to retrieve stored information from the neurostimulator, and to program detection and stimulation settings. The telemetry wand provides wireless communication between the neurostimulator and the programmer. The system and patient data can be uploaded to a central patient data management system via the web allowing the physician to monitor the patient remotely.

The stimulator delivers constant-current, biphasic, charge-balanced pulses upon detection of an seizure. The detection tools can be adjusted by the physician to optimize the trade-off between sensitivity and specificity for a given patient. Two detectors can be independently programmed for either of the two sensing channels. The device can be programmed by the physician to deliver stimulation frequencies ranging from 1-333 Hz, pulse widths from 40 to 1000 mic sec, and current amplitudes from 1-12 mA. Stimulation can be configured to apply current between any combination of electrodes and the device case. Parameters for stimulation are empirically determined, although the system is designed to limit current density to less than 25 micC/cm² per phase. In addition, programming options include

bipolar stimulation across electrode pairs or stimulating across all eight electrodes to the case.

Experience with the RNS system includes a feasibility study of 65 patients which revealed excellent safety and tolerability and preliminary evidence of efficacy. (Sun et al. 2008) An interim analysis of 39 of the subjects revealed no serious device-related unanticipated adverse events. In the first 24 patients who had complete data, the responder rate (>50% reduction in seizures) was 43% for complex partial seizures and 35% for simple partial, complex partial or secondarily generalized tonic-clonic seizures. At the time of this writing, a double-blinded, randomized, multicenter clinical trial is underway to determine whether the RNS System is safe and effective as an adjunctive treatment for medically refractory partial-onset seizures.

6. Conclusion

In spite of optimal medical management, many patients with epilepsy remain medically refractory and suffer from debilitating seizures. Many of the medically refractory patients are not candidates for surgery because of the inability to localize a resectable focus. Some of these patients may benefit from neuromodulatory treatment. A variety of targets may be suitable for implantation and no current studies exist to favor one target over another, or even one modality over another. Additional studies are needed to identify the appropriate patient population for neuromodulation, the optimal target, the best stimulation modality, and the best stimulation parameters within that modality. It may be that a complex pathologic entity as heterogeneous as epilepsy cannot be addressed via a single target or even technology. Differences in stimulation parameters within the same anatomic target make it difficult to compare the available animal and clinical studies, perhaps raising more questions than have been answered. Is unilateral DBS sufficient or is bilateral stimulation necessary to prevent seizures? What is the ideal voltage, current, and frequency of stimulation that results in suppression of seizures while minimizing damage to the underlying tissue? What is the ideal waveform? Is the most effective stimulation paradigm continuous or intermittent? If intermittent, should the stimulus be at regular intervals or closed-loop, contingent upon detection of a seizure? If the stimulus needs to be bilateral and intermittent at regular intervals, should it alternate from side to side? If so, how often? Further studies are needed to determine whether open-loop or closed loop stimulation paradigms are more effective. Ultimately, the two methods may be found to be complementary and used in differing populations of patients. It is conceivable that they may even be combined within the same patient: open-loop stimulation for seizure prophylaxis and closed-loop stimulation for acute seizure interruption. The appearance of a lesioning effect arising in some studies but not others is problematic, making it difficult to compare ON and OFF intervals. This must be resolved before DBS can be embraced as a treatment option for epilepsy.

Advanced diagnostics, including magnetoencephalography and modern functional imaging, are likely to play an increasing role in determining appropriate treatment targets. Although it has already met with some success in the clinical arena, the successful future of DBS for the treatment of refractory epilepsy is contingent on the continued collaboration of clinician and scientist. Our technical capabilities have grown at a rate that may well have surpassed our understanding of the complex neurobiology that we aim to modulate. A greater knowledge of what local electrical and neurochemical alterations have led to success

in current stimulation models will help ensure reproducibility in those to come. Understanding these relationships may enable future technologies, perhaps even nanotechnologies, to flourish in the developing field of therapeutic neuromodulation.

7. References

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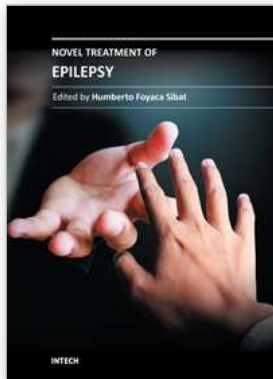
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Epilepsy continues to be a major health problem throughout the planet, affecting millions of people, mainly in developing countries where parasitic zoonoses are more common and cysticercosis, as a leading cause, is endemic. There is epidemiological 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 *in vitro* 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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