Experimental Neurology 244 (2013) 87–95

Contents lists available at SciVerse ScienceDirect

Experimental Neurology

journal homepage: www.elsevier.com/locate/yexnr

Review

# Neurostimulation in the treatment of epilepsy

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ARTICLE INFO

*Article history:*
Received 26 March 2012
Revised 4 April 2013
Accepted 8 April 2013
Available online 11 April 2013

*Keywords:*
Neurostimulation
Epilepsy
Anterior thalamic
Responsive neurostimulation
Closed loop
Vagus nerve stimulation

ABSTRACT

There is increased interest in neurostimulation as a treatment for drug-resistant epilepsy. Two large pivotal trials have recently been completed, one using bilateral anterior thalamic stimulation and another employing closed loop responsive therapy of the brain. These are potential additions to the therapeutic options for neurostimulation in addition to already approved vagus nerve stimulation. This review will address the principles of the various types of neurostimulation, the results of the pivotal trials and the important considerations for interpreting the results of these trials which differ from trials of antiepileptic drugs.



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## Introduction

Patients with partial seizures (simple and complex) comprise over 50% of patients with epilepsy (Hauser et al., 1996). In contrast to patients with primary generalized epilepsy where >80% of patients achieve seizure control, only about half of patients with partial epilepsy have their seizures controlled (Sillanpää et al., 1998). Despite the introduction in the United States of 14 new antiepileptic drugs (AEDs) since 1993, there still is a very large unmet need for patients with drug-resistant epilepsy. The major benefit of the new (since 1993) AEDs has been better tolerability and side effect profiles and more desirable pharmacokinetics, especially fewer drug interactions. Unfortunately few patients with drug resistant partial epilepsy become seizure free with the new AEDs after failing previous trials of 2 or 3 or more drugs (Kwan and Brodie, 2000). Seizure surgery can produce seizure freedom in a significant number of patients with drug-resistant partial seizures and surgery remains underutilized. Many patients, however, are not candidates for resective surgery. The lack of a major impact of the new AEDs on seizure freedom, despite many new and novel compounds with new mechanisms of action, has led to increased interest in alternative therapies such as dietary management (Kossoff and Hartman, 2012), immunotherapy (Bien and Scheffer, 2011) and newer methods of neurostimulation.

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http://dx.doi.org/10.1016/j.expneurol.2013.04.004

The concept of neurostimulation for the treatment of epilepsy is not new. Unsuccessful trials of stimulation of the cerebellum and the median thalamic nucleus have been performed. While both sites showed promise in unblinded studies (Cooper, 1978; Cooper et al., 1976; Davis and Emmonds, 1992), subsequent controlled trials failed to demonstrate significant efficacy (Wright et al., 1984). Vagus nerve stimulation (VNS) was the first approved therapy utilizing chronic stimulation, gaining FDA approval in 1997. Recently two pivotal trials of neurostimulation in humans with drug-resistant epilepsy, one employing chronic programmed bilateral stimulation of the anterior thalamus and another utilizing closed-loop responsive stimulation of intracranial structures have been completed and published (Fisher et al., 2010; Morrell and RNS System in Epilepsy Study Group, 2011). Anterior thalamic stimulation has not received FDA approval but was recently approved in Europe. The responsive neurostimulation device (RNS) was recommended for approval by a scientific advisory panel in early 2013; FDA approval is pending. In addition there are early reports of potential benefits of stimulating other extracranial sites (e.g. trigeminal nerve) (DeGeorgio et al., 2009; DeGiorgio et al., 2013; Pop et al., 2011). It is therefore timely to examine the current status of neurostimulation in the treatment of epilepsy. While some historical context will be provided, the purpose of this review is to discuss the current modalities of neurostimulation being utilized or studied as potential therapies with an emphasis on those that have completed pivotal blinded trials and involve implanted devices. The potential benefits of neurostimulation, regardless of the treatment modality, are several. Neurostimulation does not have the side effects, CNS or systemic, that AEDs have. Although not formally assessed, it is reasonable to assume that there is no teratogenicity associated with neurostimulation. The mechanisms of action of neurostimulation, although not established, are probably distinct from those of AEDs. Neurostimulation also occurs automatically, whether programmed or open loop and while patients with VNS can employ magnet activation, this is a supplemental therapy; benefit was demonstrated without patient activation. When one considers that trials of additional AEDs add to the medication burden with attendant potential additive side effects, the attraction of neurostimulation in patients who are not good resective surgery candidates is obvious (Table 1).

## Neurostimulation: types and theoretical considerations

Neurostimulation can be classified in two ways, the location of the stimulation target (intracranial or extracranial) and the method of stimulation (chronic programmed or responsive, closed loop). The theories behind the mechanisms of action of each type of therapy are different. The concept of any type of neurostimulation for control of epilepsy might at first consideration appear counterintuitive. Epileptic seizures, after all, are reflections of increased neuronal network excitation and increased synchronized activity in the brain. But an appreciation of the basic concepts of partial epileptic seizures provides support for these therapies. The table lists some characteristics of the most important neurostimulation modalities.

The normal, non-epileptic brain has continuous background activity; all waveforms seen in the normal EEG, waking and sleep, reflect synchronous activity of neuronal ensembles. Therefore synchronous activity in the brain is not abnormal per se. An epileptic seizure, however, represents a brief departure from this normal background synchronized activity to an abnormal state. In the case of primary generalized epilepsy (e.g. absence, generalized tonic–clonic) this may represent a rather abrupt switch between two states (Suffczynski et al., 2004). With focal or partial epilepsy the seizure begins at the seizure onset zone and then gradually propagates regionally or ultimately secondarily generalizes. Since most partial seizures are symptomatic or cryptogenic, it is reasonable to hypothesize that the seizure onset zone represents an abnormal neural network, predisposed to produce epileptic seizures. This might reflect such changes as mossy fiber sprouting in mesial temporal structures (Zhang et al., 2012) or alteration of interneuronal inhibition in post-traumatic epilepsy (Gupta et al., 2012). A recent report using neural network modeling demonstrates how simple normal background input into such an abnormal network can occasionally trigger a partial epileptic seizure, something that would not happen in a normal neural network (Anderson et al., 2012).

An epileptic seizure, whether partial or generalized, is characterized by a brief, transient period of abnormal, increased focal, regional, or generalized neural network synchronized activity. Mesial temporal lobe partial seizures typically have a median duration of only 106 s; neocortical extratemporal onset partial seizures are even shorter, with a median duration of 78 s (Afra et al., 2008). Yet even these brief events, if they produce alteration of consciousness, can have a major impact on the quality of life of patients with uncontrolled epilepsy.

The goal of any therapy is to prevent disabling seizures (i.e. those with altered consciousness or motor activity that affects function). In theory this can be done by preventing seizure occurrence, or by limiting seizures to brief subclinical electrical discharges or simple partial seizures. AEDs can control or reduce the frequency of partial and generalized seizures by various alterations of cellular or synaptic function (e.g. reduced repetitive firing, neuromodulation of synaptic vesicular release, augmentation of GABAergic inhibition).

Whether the brains of patients with epilepsy have increased focal or regional synchrony is not established. The principle behind chronic programmed stimulation, whether extracranial (e.g. VNS) or intracranial (e.g. anterior thalamus) is to modulate this background activity so that an epileptic seizure is less likely to occur. This could occur by producing network desynchronization or reducing background synchronization or modulating specific pathways.

Epileptic seizures are, however, self-limited events even without intervention. In this way they differ from cardiac arrhythmias. Intracranial recordings reveal that seizures often end synchronously in all brain regions, even those remote from the seizure onset zone (Afra et al., 2008). These observations suggest that early responsive therapy might have

**Table 1**
Types of neurostimulation therapy for epilepsy.

| | Vagus nerve | Anterior thalamic | Responsive neurostimulation |
|---|---|---|---|
| Target | Extracranial, | Intracranial, | Intracranial, |
| Location | Left vagus nerve | Bilateral anterior thalamus | Site varies depending upon presumed seizure focus |
| Stimulation | Programmed periodic stimulation | Programmed periodic stimulation | Responsive intermittent |
| | Open-loop | Open loop | Closed-loop |
| Seizure detection required | No | No | Yes |
| Seizure data recorded | No | No | Yes, downloadable |
| Patient activation possible | Yes | No | No |

Characteristics of the three types of neurostimulation therapy for epilepsy that are either FDA approved (vagus nerve) or have completed pivotal blinded trials (anterior thalamic and responsive neurostimulation).

the potential to produce early termination of epileptic seizures. Indeed the concept of closed-loop responsive therapy is not to prevent seizures but to produce early termination of the focal seizure before it propagates to become a disabling event with alteration of consciousness. To do this requires early detection of the seizure so that early intervention can occur. Even recognizing that such early detection is just that, i.e. not seizure prediction, there are a number of challenges in accomplishing this goal. Recurrent seizures from a given seizure focus in a patient tend to have similar patterns of onset if analyzed by time-frequency decomposition (Jouny et al., 2007). The onset of the seizure is characterized by an increase in signal complexity even when the signal appears to have a single predominant frequency (Jouny and Bergey, 2012). Improving early seizure detection is important if closed loop therapy is to be specific, if therapy is to be directed to activity that is destined to evolve into seizure activity (Jouny et al., 2011) (Fig. 1).

Since epileptic seizures represent transient periods of increased excitation and increased neuronal network synchrony, it is tempting to think that early termination of these seizures would require selective enhancement of interneuronal inhibition. Excitatory neurons comprise 80–90% of the neurons in the human brain (Gulyas et al., 1999). Any intracranial stimulation is therefore going to result in stimulation of mixed neuronal populations (excitatory and inhibitory). Studies in neuronal network models have shown, however, that spontaneous seizure cessation can occur in networks that have no inhibition (Kudela et al., 1999) and that external stimulation can result in seizure termination in networks with or without inhibition (Franaszczuk et al., 2003). Therefore seizure termination, whether spontaneous or evoked, does not require network inhibition and external excitatory stimulation can result in early seizure termination without needing to selectively enhance inhibition. Indeed the mechanism of seizure termination by responsive stimulation is not resolved, but may result from disruption of seizure dynamics and a net decrease of neuronal network activity.

## Extracranial programmed stimulation: vagus nerve stimulation

VNS therapy is the first FDA approved neurostimulation therapy for epilepsy. The early studies of VNS were done in cats (Bailey and Bremer, 1938; Chase et al., 1967; Zanchetti et al., 1952). Studies by Chase et al. (1967) reported that stimulation of the vagus nerve desynchronized the EEG in cats, but this has not been demonstrated in humans (Salinsky and Burchiel, 1993). Later Fernández-Guardiola et al. (1999) demonstrated that kindling of the amygdala, also in cats, could be reduced with VNS. The actual mechanism of action of VNS is not established. The ascending pathway from the vagus nerve is a polysynaptic path that involves the locus coeruleus and benefits from VNS therapy are undoubtedly synaptically mediated. Whether the beneficial actions are at the level of the cortex, thalamus, or involve brainstem structures is not established. Studies of changes in regional cerebral blood flow with PET during VNS therapy revealed changes in bilateral thalamic regions that correlated with efficacy (Henry et al., 1999). A recent report (Nichols et al., 2011) found that VNS increased and decorrelated spontaneous multi-unit activity in rat auditory cortex and suppressed entrainment to repetitive noise burst stimulation. These effects on cortical excitability and synchrony are thought to be due to activation of muscarinic receptors because the changes were blocked by the muscarinic antagonist scopolamine. Previous studies have suggested that the actions of VNS are mediated by enhanced noradrenergic activity (Berridge and Foote, 1991; Follesa et al., 2007; Roosevelt et al., 2006; Smith et al., 2006). Increased norepinephrine release correlates with VNS anti-seizure activity in a limbic seizure model (Raedt et al., 2011) and lesioning the locus coeruleus reduces VNS seizure attenuation (Krahl et al., 1998). As Nichols et al. (2011) comment, however, lesions of the locus coeruleus can affect downstream acetylcholine release. Additional studies have suggested that VNS can modify brain plasticity, a novel concept (Engineer et al., 2011; Shetake et al., 2012); VNS induces increases in hippocampal neurogenesis in rats (Revesz et al., 2008).

Approval of VNS therapy was based predominantly on two randomized controlled trials E03 (The Vagus Nerve Stimulation Study Group, 1995) and E05 (Handforth et al., 1998) in 114 and 199 patients respectively. The two randomized arms included high and low stimulations. The high stimulation group received stimulation with output currents up to 3.5 mA, 30 Hz, 500 μS pulsewidth, with 30 s on time and 5 min off time. The low stimulation arm had similar output currents, but a frequency of 1 Hz, pulsewidth of 130 μS, on time of 30 s, and off time of 180 min. In contrast to intracranial stimulation, where stimulation is not felt by the subject, VNS therapy is appreciated by the patients so a true placebo arm would have compromised the blind.

Only a limited period of time (2 weeks) was available for adjustment of stimulation parameters. The assessment period was 12 weeks and the primary outcome measure was percent change in seizure frequency. In the E03 study the high stimulation group had a 24.5% mean reduction in seizures (compared to 6.1% in the low stimulation group; $p = 0.01$). In the E05 study the high stimulation group had a 27.9% mean percent decrease in seizure frequency (15.2% in low stimulation group; $p = 0.04$). In the E03 study the high stimulation group had a 27% responder rate (patients with >50% reduction in seizures) compared to 13% of patients in the low stimulation group. In the E05 study the responder rate was slightly higher (34%). Very few patients became seizure free, but these were patients with long-standing, highly drug resistant epilepsy who were not resective surgery candidates.

The patient populations, study duration, and outcome measures for the pivotal VNS studies (and other studies of neurostimulation) are similar to those for AED trials. While one could argue that the blind was compromised by a 3 h interval between stimulations in the low intensity group, a similar argument can be made for drug trials where if the active compound produces side effects compared to placebo, the blind may not be totally preserved and arguably there is no better trial design. Interestingly the percent change in total seizure frequency, the responder rates, and the observed benefits in the active control arm of the VNS studies are very similar to what has been observed with new AED trials. Efficacy with the VNS and other types of neurostimulation appear to improve with time, after the blinded period, with later responder rates exceeding 50%. It has been suggested that this represents

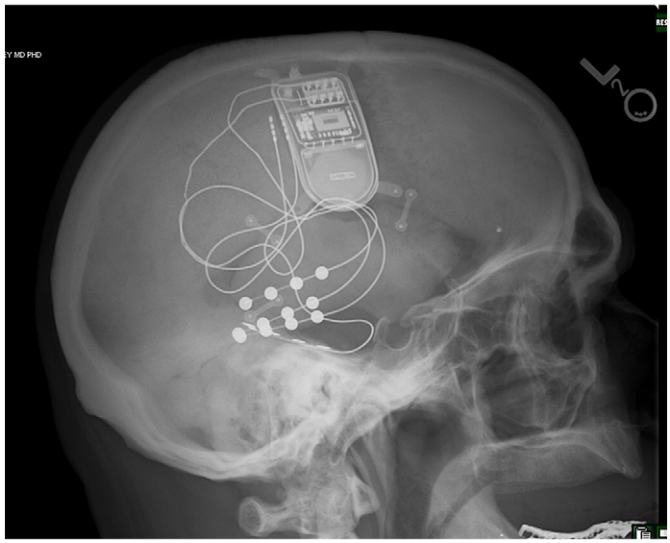

**Fig. 1.** Skull film of a patient with a NeuroPace responsive neurostimulation device. The patient had temporal lobe neocortical onset seizures. Four subdural strips are shown, two of which (one lateral, one basal temporal) are connected to the RNS. The RNS resides in a ferrule in a skull recess. The device can be seen containing a battery, digital processor, programmable chip, memory chip, and connectors.

a type of neuromodulation not seen in AED trials. While this may be the case, only a longer blinded trial period (when no adjustments in other therapy are allowed) can conclusively demonstrate this. Whether a longer period to adjust stimulus parameters and tolerability would have resulted in improved efficacy is also not known. It has been mentioned that VNS therapy is not transparent; it is appreciated by the patient. But the side effects of hoarseness and cough are dramatically reduced with time, particularly after the first year (Morris and Mueller, 1999). Although not widely used because the trial results are controversial, VNS is FDA approved for treatment refractory depression (Martin and Martin-Sánchez, 2012; Rizvi et al., 2011).

### Extracranial programmed stimulation: other

With the success of VNS therapy, it is not surprising that other sites for external chronic programmed neurostimulation are being investigated. Currently stimulation of the trigeminal nerve is being most actively pursued. The trigeminal nerve projects to brainstem structures distinct from those activated by VNS, but like the VNS, then has supratentorial influences. Stimulation of the trigeminal nerve, while perceived by the patient, does not produce the hoarseness or cough that may result from vagus nerve stimulation. Preliminary unblinded studies of transcutaneous stimulation of infraorbital and supraorbital branches of the trigeminal nerve suggest efficacy and tolerability (DeGeorgio et al., 2009; Pop et al., 2011). A recent report (DeGiorgio et al., 2013) of a randomized controlled trial of trigeminal nerve stimulation in 50 patients with drug-resistant partial seizures found no significant overall change in the responder rate (>50% reduction in seizure frequency) of treated patients compared to controls, but did find a significant within-group improvement in responder rate over the 18-week treatment period (from 17.8% to 40.5%). These preliminary results will lead to a larger controlled trial in the future. The mechanism of action of any potential benefit of trigeminal nerve stimulation remains to be elucidated.

Small uncontrolled studies of repetitive transcranial magnetic stimulation (rTMS) have been reported to benefit patients with drug-resistant partial seizures (Kimiskidis, 2010; Nitsche and Paulus, 2009). The repetitive stimulation paradigm induces changes in cortical excitability that last beyond the period of actual stimulation (Hoogendam et al., 2010). Like other neurostimulation modalities, the exact parameters for rTMS are still being explored (Rubens and Zanto, 2012). Large controlled trials of this treatment modality have not yet been performed.

### Central programmed stimulation — early studies

With the modest, but significant benefits of stimulation of the vagus nerve, it is reasonable to postulate that stimulation of intracranial structures might demonstrate improved efficacy. Central stimulation, while requiring surgery to implant the electrodes, does have the benefit of being transparent; the patient does not feel the stimulation since the brain is pain insensitive, in contrast to VNS stimulation which is perceived to some degree by the patient. This lack of central sensation also makes it easier to design blinded trials since the blind is more easily preserved between active and control groups.

As mentioned, cerebellar stimulation was employed in the 1970s (Cooper, 1978; Cooper et al., 1976) in an attempt to treat epileptic seizures and uncontrolled studies suggested efficacy. Over 600 patients had implantation of cerebellar stimulators, not all for epilepsy; it was also used to treat spasticity. Electrodes were placed on the upper surface of the cerebellum through burr holes or a craniotomy and stimulus intensities of 1–9 mA, 10 pulses per second were administered. When a blinded trial was performed, however, there was no significant reduction in seizures for any patients, despite most reporting subjective improvement (Wright et al., 1984). Interestingly the principle behind the earliest studies with cerebellar stimulation was to increase frontal lobe inhibition since the output from the cerebellum is exclusively inhibitory (GABAergic) and projects to the motor and premotor areas. One reason that this therapy may have failed is that even at a resting state, Purkinje cells, which provide the sole output of the cerebellum, fire rapidly (Holdefer and Miller, 2009), so chronic low frequency stimulation may not have increased inhibitory outflow much. It is worth noting, however, that the failed blinded trial of cerebellar stimulation only involved 12 patients. Whether a controlled trial with a large number of patients (e.g. 100–200) would have yielded different results is not known. Recent controlled trials of central neurostimulation if limited to 12 patients are unlikely to have been sufficiently powered to demonstrate efficacy.

The rationale behind stimulation of the thalamus is that midline thalamic nuclei have strong connections with limbic regions and the thalamus is an important relay for afferents to the cortex. Electrical stimulation of the reticular nucleus in the rat suppressed kindled limbic seizures (Nanobashvili et al., 2003). High frequency stimulation of the anterior nucleus of the thalamus can raise the clonic seizure threshold, although low frequency stimulation may be proconvulsant (Mirski et al., 1997). The cortical EEG is highly coherent with anterior thalamic activity (Mirksi et al., 2003; Wennberg and Lozano, 2003) and anterior nuclear stimulation increases the threshold for motor cortex excitability (Molnar et al., 2002). Stimulation of the thalamus can influence the cortical EEG (Wennberg, 2008).

Before the more recent trials of programmed stimulation of the anterior thalamus (discussed below), trials stimulating the central medium nucleus of the thalamus were tried. Unblinded studies suggested that chronic intermittent stimulation of the centromedian thalamic nucleus was beneficial, being most effective for generalized tonic–clonic seizures and atypical absence (Cukiert et al., 2009; Velasco et al., 2001, 2001) although an earlier double-blind trial of centromedium stimulation in a small trial with only 7 patients showed a nonsignificant reduction in seizures with no patient having greater than 50% reduction in the open label period (Fisher et al., 1992). Stimulation of the thalamus today focuses on anterior thalamic stimulation. There is considerable experience with deep brain stimulation of the thalamus for movement disorders.

### Central programmed stimulation — anterior thalamic

Early reports of anterior thalamic stimulation in humans with drug resistant epilepsy suggested efficacy (Kerrigan et al., 2004). Recently the results of a well designed multicentral trial of anterior thalamic stimulation were reported (Fisher et al., 2010). A total of 110 patients at 17 sites were entered into this blinded trial. These were highly refractory patients, 54% had previous epilepsy surgery or VNS therapy. Patients were required to have focal or partial seizures, but could have multiple seizure foci. During the 3 month blinded phase of the trial, the entire treatment group had a significant 38% reduction, compared with 14.5% in the placebo group. Both complex partial seizures and secondarily generalized seizures significantly improved with stimulation during the blinded period. Patients ($n = 33$) with temporal lobe epilepsy had a greater seizure reduction with stimulation, 44% during the blinded period compared with the 22% reduction in seizure frequency observed in control patients with temporal lobe epilepsy ($n = 29$, $p = 0.025$). Anterior thalamic stimulation was safe; there were no symptomatic hemorrhages or death. Although there was a suggestion of possible worsening of depression or memory, this was not confirmed by objective testing.

Like other trials of neurostimulation, the efficacy of anterior thalamic stimulation increased over time in the open label period with 41% median seizure frequency reduction at 13 months, and 56% at 2 years of long-term follow-up. The responder rates (patients with >50% reduction in seizures) also increased over time, reaching 43% at 13 months, 54% at 2 years, and 67% at 3 years (Fisher et al., 2010). Eight patients were seizure free for at least one year. These changes

occurred during the open label extension when adjustments in medications could also be made, recognizing that these patients had highly drug-resistant epilepsy.

Interestingly, like the trial of closed loop responsive therapy (see below), there was an apparent early sham effect. During the first month after implantation, before activation of stimulation, both groups (those randomized to stimulation and control) experienced a virtually identical reduction (~20%) in seizure frequency. During the trial period, the control group gradually had more seizures, while the active stimulation group had a progressive reduction in seizures (Fig. 2). The mechanism of this transient sham implantation effect is not known but is seen in other trials of neurostimulation as well (see below).

### Central stimulation — closed loop responsive

The concept of closed loop responsive stimulation is an attractive one. Instead of preventing seizures, closed loop therapy would respond shortly after seizure onset to provide therapy that would lead to early seizure termination before the seizure evolves to a disabling seizure (e.g. with altered consciousness). The underlying principle is that seizures are intrinsically self-limited events and that early intervention can result in reduced seizure duration. While any therapy (e.g. cooling, focal application of medication) could be part of closed loop therapy, the discussion here will be limited to closed loop stimulation.

Early seizure detection requires application of detection algorithms that have high sensitivity. Reliable early seizure detection is aided by intracranial electrodes that minimize artifact and the fact that seizure onset from a single focus in a given patient is fairly stereotyped both with regard to time-frequency signal changes and changes in complexity (Jouny and Bergey, 2012). This allows detection algorithms to be tuned for a given patient's seizures, increasing both sensitivity and specificity. The challenge for these detection algorithms is that detection must be made early in the seizure. Detecting seizures in an epilepsy monitoring unit can use the entire seizure and look back retrospectively. If, however, seizures need to be detected on-line within several seconds before regional seizure propagation, this requires that the recording electrode be close to the seizure onset zone and the detection algorithms need to be designed for such early detection. This, by necessity sacrifices specificity, since epileptiform activity may be detected and therapy applied when no evolution to a clinical seizure was destined to occur.

Recently a multi-center, double-blind, randomized controlled trial of responsive stimulation for the treatment of drug-resistant partial seizures was completed and reported (Morrell and RNS System in Epilepsy Study Group, 2011). These studies followed initial proof-of-principle studies to show that cortical stimulation could terminate after discharges produced during function mapping (Karceski et al., 2000; Lesser et al., 1999). As mentioned above, there is evidence from neuronal network models that excitatory stimulation can terminate burst activity even in the absence of inhibition. Subsequent unblinded safety and feasibility studies were performed in adults with drug-resistant partial epilepsy; these studies supported safety and efficacy (Bergey et al., 2002, 2006). As with thalamic stimulation, information regarding safety was drawn from previous experience in humans with deep brain stimulation for movement disorders.

The pivotal, controlled trial had 191 patients from 32 sites. Like the anterior thalamic stimulation trial, these patients had highly drug-resistant partial epilepsy. Patients could have one or two discrete seizure foci, but no more and the seizure foci had to be sufficiently well localized to target therapy although not all patients had previous intracranial monitoring. In the group 32% had previous epilepsy surgery, 34% had prior VNS (this was removed per protocol) and the average number of AEDs was 2.8. The primary outcome variable was seizure reduction. A statistically significant reduction in seizures was seen with 38% reduction during the blinded phase compared to 17% in the sham group in the 12-week blinded period (Fig. 3). Like the trial of anterior thalamic stimulation, there was an early sham effect prior to onset of stimulation and then subsequent separation of the treatment and sham group during the blinded evaluation period. During the open label period, those previously in the sham group then experience seizure reduction that subsequently approaches the degree seen in those initially receiving treatment. Also, similar to the anterior thalamic trial, there is

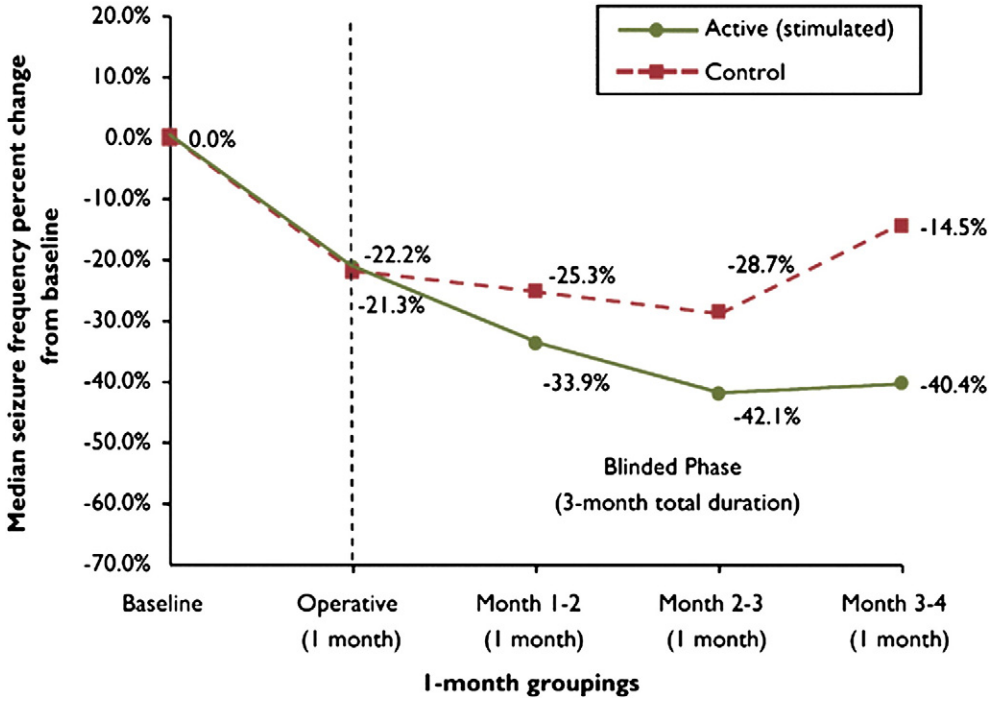


**Fig. 2.** Electrical stimulation of the anterior nucleus of the thalamus (SANTE trial) median seizure frequency (n = 108 patients). Note the reduction in median seizure frequency in the first month after implantation, before active stimulation was begun, for patients randomized to both control and active stimulation groups (Fisher et al., 2010) (Used with permission).

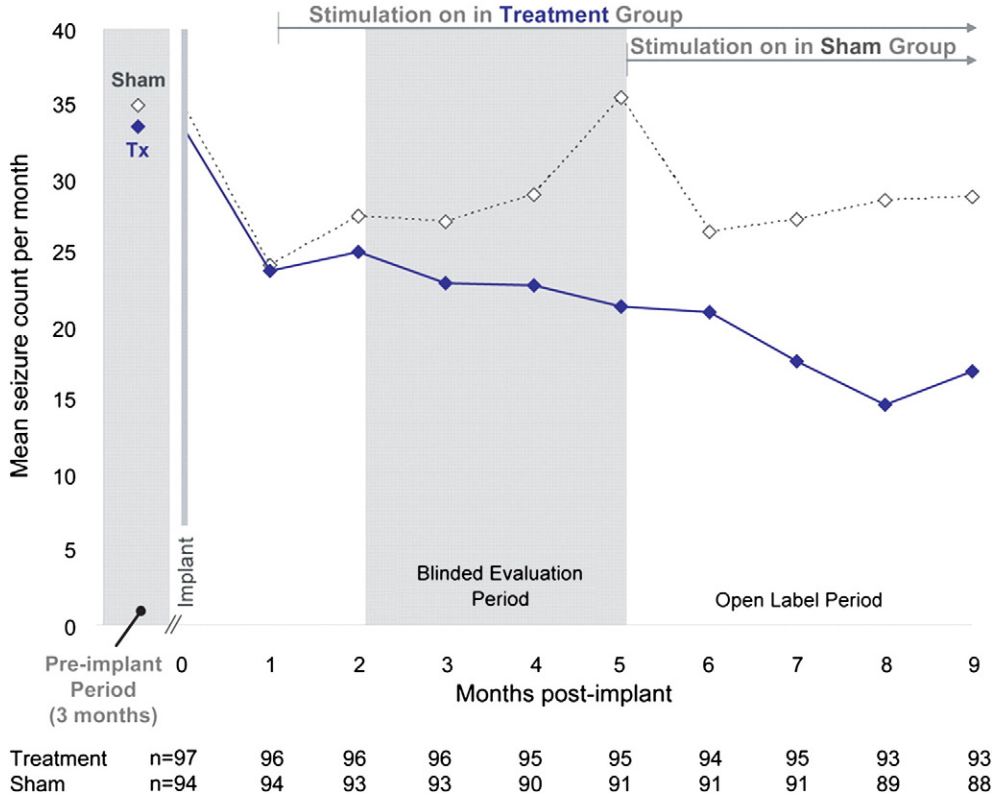


**Fig. 3.** Mean disabling seizures by month in the RNS trial, observed data N represents the number of subjects with seizure data during that interval. Note the reduction in seizures seen in all patients in the first month after implantation, before any active therapy. Mean seizures in the sham group then begin to rise during the blinded evaluation period and then decrease in the early open label period when the sham group begins to receive stimulation. In later months of the open label period (not shown) the mean seizure counts in both groups are similar (Morrell and RNS System in Epilepsy Study Group, 2011) (Used with permission).

progressive improvement with time during the open label period with median seizure reduction reaching 50% after two years. There was excellent retention, with a retention rate of >90% at 3 years, better than retention in the open label period of any new AED trial. These patients did have the option to have the device turned off or not to have the device replaced when battery life expired (always within 3 years) so these high retention rates reflect patient satisfaction with the overall response and side effect profile.

Interestingly since the seizure detection algorithms, even when tuned for a given patient, need to be very sensitive for early detection, it is not uncommon for detections and therapy to be hundreds of times per day. Because of the brief stimulus duration, the total amount of therapy per day is still relatively short. These detections are not false detections since they are triggered by epileptiform activity, but obviously most of these detections were not destined to evolve into clinical seizures. There is no evidence that these additional therapies are detrimental and indeed they could be beneficial. Indeed the only apparent negative to frequent detections and therapies is shortened battery life. The detection algorithm when adjusted can be applied to previously recorded seizures to determine if early detection is improved. Recorded long epochs may reveal unreported seizures.

In all trials of the responsive neurostimulation system (n = 256) infection and hemorrhage rates were similar to those for comparable procedures (e.g. implantation of electrodes for presurgical evaluations, deep brain stimulation for Parkinson disease or epilepsy).

## Central stimulation — other

Drawing on the experience of stimulation of the subthalamic nucleus for movement disorders, limited trials have been employed in patients with epilepsy. The subthalamic nucleus is thought to activate the nigral control system (Deransart et al., 1998) and may act to prevent secondary generalization. Small studies in humans suggest efficacy (Chabardès et al., 2002; Wille et al., 2011) of stimulation of the subthalamic nucleus in humans but no large controlled trials are ongoing.

The hippocampus would seem to be an appropriate target for neurostimulation since mesial temporal lobe epilepsy is a common cause for complex partial seizures. Indeed some of the patients in the responsive neurostimulation trial had implantation of depth arrays in mesial temporal structures. Animal studies suggest chronic stimulation of mesial temporal structures could be beneficial (Rashid et al., 2012). Some unblinded human studies have been done and suggest possible efficacy (Boëx et al., 2011; Boon et al., 2007, 2008) but no pivotal controlled trials have been done.

Concern has been raised that stimulation of brain structures could trigger seizures; certainly this can occur during presurgical cortical mapping studies. In the trials of both anterior thalamic and responsive neurostimulation, there was no clear evidence of seizure exacerbation except for isolated instances. This is easily resolved by adjustment of stimulus parameters. Concern about recurrent stimulation kindling the brain or producing other negative sequelae has not been demonstrated. Indeed a recent report (Suthana et al., 2012) demonstrated memory enhancement with deep-brain stimulation of the entorhinal area.

## Stimulus parameters

There is a suggestion from some animal studies that higher frequency stimulation (e.g. 130 Hz) is more effective than lower frequency (e.g. 5 Hz) stimulation (Wyckhuys et al., 2010). Studies in the anterior thalamus have suggested that low frequency stimulation may be detrimental (Mirski et al., 1997). In animal models of temporal lobe epilepsy, however, some have found low frequency beneficial (Rashid et al.,

2012). Stimulus frequency does appear to be an important stimulation parameter (Rajdev et al., 2011).

In the pivotal anterior thalamic stimulation trial (Fisher et al., 2010) stimulation was performed at 5 V, 0.9 ms pulses, 145 Hz, on for 1 min, off for 5 min. In the responsive neurostimulation pivotal trial (Morrell and RNS System in Epilepsy Study Group, 2011) pulse durations of 160 μS and stimulus durations of 100–200 ms were used, but the investigators could chose the stimulus intensity (up to 12 mA for all contacts stimulated), and could vary the stimulus frequency (100–200 Hz were most commonly used). Stimulus parameters could be adjusted at each visit in the RNS study, whether in the blinded or later open label period. While it is probable that the stimulus parameters may be critical for maximal response, the optimal stimulus parameters, whether for responsive stimulation or chronic programmed stimulation have not be definitively determined. It is quite possible that the best stimulus parameters may differ depending upon the brain region, whether chronic or responsive stimulation is used, and may also be species dependent. In responsive stimulation studies, there may also be phase dependency. Neuronal network models may provide some insight into optimizing stimulation parameters (Anderson et al., 2009).

## Trial design and assessment of efficacy

As is the case with antiepileptic drug trials, reduction in absolute seizure numbers and responder rate (percentage of patients who experience a >50% reduction in seizures) during the blinded period are the outcome variables. In AED trials assessment of true efficacy can be compromised by a number of variables. If the doses of the trial agent are too low, efficacy may be underestimated. If AED doses are too high, or titration is too rapid, patients may withdraw from the trials due to side effects and be counted as failures. While placebo responder rates in AED trials in the past were typically in the range of 10%, recent trials, often with sites in countries not previously utilized have had placebo responder rates >20%. Obviously high placebo responder rates compromise power calculations and can have profound effects on measures of significance. Nevertheless a well designed trial (e.g. levetiracetam which used doses of 1000–3000 mg/day) can provide a good assessment of efficacy within the blinded period (typically 12–188 weeks). Responder rates with new AEDs are typically in the range of 25–50%; few of these very drug resistant patients become seizure free.

Assessment of efficacy of neurostimulation, although employing similar outcome measures, is different than AED assessment. With these implanted devices with no drug related side effects, few patients withdraw during the treatment period. Surprisingly in both the anterior thalamic and responsive neurostimulation trials there were positive sham responders before the devices were turned on to stimulate. The major challenge to assessment of neurostimulation is the fact that the optimal stimulation parameters are not known. Therefore the trial design must employ a best estimate of these parameters (as in anterior thalamic stimulation) not accounting for patient to patient variability, and there is a limited period of time (the blinded treatment period of 12–16 weeks) to make adjustments. It is therefore entirely possible that optimal stimulus parameters may not have been achieved during the blinded period. With various types of neurostimulation (VNS, AT, RNS) there is a gradual improvement in responders over a long period of time, increasing to 50–60% at one year. While this improvement is difficult to accurately assess since adjustments in other therapies (e.g. AEDs) can be made outside the blinded period, this has been a consistently observed phenomenon in all of the large neurostimulation trials. Whether this reflects improved stimulation parameters, neuromodulation, or chronic beneficial effects of repetitive stimulation, is not known. In the trials of anterior thalamic stimulation and responsive stimulation, the patients had highly refractory partial epilepsy, with more than half having had prior epilepsy surgery or implantation of the VNS. These patients had long histories of seizures, frequent seizures, and were on multiple AEDs.

VNS implantation is a slightly invasive, outpatient surgery. Implantation of anterior thalamic stimulators or the responsive stimulation device may require an overnight hospital stay and does involve implantation of intracranial electrodes. Balancing the more invasive nature of the latter two modalities is the later benefit of transparent therapy which the patient does not feel.

As mentioned previously, the average new AED trial in adults with drug-resistant partial seizures will produce seizure reductions of 20–50% during blinded trial periods. These AED responses are dose dependent; higher doses produce improved response but at the expense of increased side effects. Should neurostimulation devices that require intracranial implantation be held to a higher standard than AEDs, or is the benefit of no drug related side effects sufficient to balance the slightly increased risk of surgery? If AED trial doses are chosen wisely, one can reasonably infer that the responses seen are the best that can be hoped for. In the case of neurostimulation, however, as mentioned above, the optimal stimulation parameters may differ from patient to patient and may not be known or implemented during the brief trial period. Should trials of neurostimulation employ longer blinded periods than those for AEDs for this reason?

Seizure frequency is an important predictor of impaired health related quality of life (HRQOL) and even infrequent seizures can have a negative impact (Gilliam, 2002). The number of seizure free patients in any of the trials of neurostimulation is low, in part because of the patient populations enrolled (i.e. highly pharmacoresistant and not good candidates for resective surgery). In a recent study of over 900 patients with pharmacoresistant epilepsy, adverse events of medication and depressive symptoms were more important determinants of HRQOL than seizures themselves (Luoni et al., 2011). These authors point out that when seizure freedom cannot be achieved, reducing AED toxicity may still be beneficial and indeed may be more important than reducing seizure frequency. As mentioned, neurostimulation has as an important benefit, the lack of drug related side effects.

## Current status of neurostimulation for the treatment of epilepsy

Vagus nerve stimulation, anterior thalamic stimulation, and closed-loop responsive stimulation all have demonstrated significant efficacy in well-designed controlled trials. Interestingly the recent results for anterior thalamic stimulation and responsive neurostimulation are remarkably similar in comparable patient populations with highly drug resistant partial seizures. Although one or the other might have hypothetical advantages, at present there is no evidence to recommend one modality over the other. While patients with either anterior thalamic and responsive stimulation had seizure reductions during the blinded period that were somewhat greater than VNS, until a randomized comparative trial is performed, it is not possible to claim that one treatment is preferable. Whether there are subsets of patients (e.g. mesial temporal onset) who benefit from one device or another is also not established.

At present the VNS is FDA approved in the US and other countries, anterior thalamic stimulation is approved in Europe but not in the United States. Responsive closed loop stimulation is currently under FDA review, having received a favorable endorsement by an advisory board in February, 2013. While it would be easy to merely say that the responses with these therapies are no different than those seen with new AEDs, one hopes that with time improved selection of patients and stimulus parameters can improve upon the current results. The phenomenon of gradual improvement with time seen with all types of neurostimulation further fuels this hope.

## Acknowledgments

GKB serves as site PI for the NeuroPace responsive neurostimulation trial but receives no support from NeuroPace.

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