Efficacy of electrical brain stimulation in epilepsy

The brain, in a similar fashion to the heart, is an electrical organ. Antiepileptic medication fails to control seizures in approximately 30% of patients with epilepsy, requires local concentration in the brain following gastrointestinal absorption and has frequent, sometimes serious, side effects. Using electrical brain stimulation therapy to directly modulate neuronal discharges (the origin and basis of seizure activity) holds much promise to reduce seizures in a substantial proportion of patients with refractory epilepsy. Electrical brain stimulation is at the interface of biology, medicine and engineering.

KEYWORDS: closed loop ■ deep-brain stimulation ■ epilepsy ■ local ■ neuromodulation ■ neurostimulation ■ open loop ■ remote ■ vagus-nerve stimulation

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Approximately 30% of epilepsy patients do not respond to antiepileptic medication, and often require polytherapy and suffer its side effects [1]. Epilepsy therapeutics has seen increasing numbers of antiepileptic drugs, without an increased level of efficacy [2]; therefore, alternative treatments are needed. Based on experimental evidence that electrical stimulation of various targets can suppress epileptiform activity or seizures, electrical stimulation for epilepsy has been explored for decades. With rapid advances in biomedical engineering, interest has grown in using electrical devices to counter epilepsy, reduce pharmacological dependence and improve quality of life. Most devices consist of computer components and a battery, with one or more leads extending to the target area. Currently, vagus-nerve stimulation (VNS) is the only US FDA-approved device for the treatment of epilepsy. Electrical stimulation for epilepsy may be appropriate in those patients who are resistant to antiepileptic drugs or those who are not candidates for resective epilepsy surgery. Currently, the goal of this therapy is to reduce seizure frequency or intensity; it is not expected to be curative and, in most cases, does not result in complete seizure freedom. This article reviews our current knowledge of electrical stimulation in epilepsy and looks forward to an expansion of approved devices including deep-brain stimulation (DBS) and responsive neurostimulation (RNS).

Stimulation paradigms

Each electrical device for epilepsy has programmable settings that control its output and determine its effect on neuronal tissue. These include current, pulse width, frequency and polarity. In addition, the timing (open or closed loop) and localization (whether remote or local to the target) of the stimulus also determine its effect. Consideration of these factors will allow a structured presentation of the various forms of electrical brain stimulation.

■ Stimulation parameters

The therapeutic stimulation parameters that are used have been derived primarily by trial and error, and the mechanisms by which electrical stimulation may benefit patients with seizures are still poorly understood [3–5]. Systematic data on different stimulation parameters at different conditions are missing.

Alternating current versus direct current stimulation

Application of alternating current has been the most common technique used in brain stimulation. However, recent *in vitro* [6] and *in vivo* [7] studies demonstrated that direct current (DC) stimulation may be a feasible alternative method for modulation of epileptiform events.

Monopolar versus bipolar stimulation

This stimulation parameter seems to be a crucial factor for selective activation of neuronal populations [8]. The degree and depth of propagation of current outside the area of study, and the size of activated neuronal tissue may be considerably affected by the polarity of the stimulus.

Stimulation frequency

Anti- or proconvulsant effects of electrical brain stimulation depend on the stimulation frequency.

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So far, frequencies from 1–800 Hz have been used [9]. In some brain regions, increasing stimulation frequency tends to induce a diminishing anticonvulsant effect that becomes proconvulsant at high frequencies [10]. Furthermore, different stimulation frequencies may selectively influence different types of seizures [9]. Most evidence suggests that high frequencies, of approximately 130 Hz, are more effective at reducing seizures and interictal activity than low frequencies (<5 Hz) [11]. However, some authors suggest that low-frequency stimulation (LFS) will be beneficial in selected settings as this could decrease energy consumption and increase battery life [12].

Intensity

The intensity of stimulation is defined by the product of pulse width and voltage. Effectiveness, as well as side effects, depend on this stimulation parameter [13]. As intensity increases, current may spread outside the area under study, increasing the risk of clinical side effects. Low stimulation intensity might not be effective enough to suppress an epileptic seizure.

Waveform

Biphasic stimulation with balanced anodal and cathodal waveforms is recommended to avoid accumulation and leakage of current.

Repetition pattern

Regular versus irregular and continuous versus intermittent patterns can be applied. In order to minimize adaptation to the stimulus, intermittent breaks lasting 1 min to several hours have been used [5].

■ Timing of the stimulus

Open-loop stimulation

During open-loop stimulation, the target is stimulated continuously regardless of seizure activity, in other words, without feedback. There may be off periods without stimulation or some adjustment of frequency.

Closed-loop stimulation

During closed-loop stimulation, there is a circuit of seizure detection, analysis and recognition, followed by the delivery of a stimulus in response to epileptiform activity.

■ Localization

Electrical stimulation can be applied either to the epileptic focus itself (local) or to distant brain areas (remote). Thus, 'local' refers to refers to stimulation paradigms where the effect mainly relies on current applied to local cells, whereas 'remote' stimulation most likely exerts influence via afferent inputs and passing fibers [14].

Local

According to computational models of neuronal stimulation, each neuron or part of a neuron surrounding the stimulation electrode will be influenced by depolarizing, as well as hyperpolarizing effects [15]. Therefore, a neuron can potentially be excited or suppressed by extracellular stimulation. *In vitro* experiments have demonstrated that extracellular high-frequency stimulation (HFS) of hippocampal structures reduces the amplitude of epileptiform discharges by hyperpolarization of the target neurons [16]. This may be caused by increased extracellular potassium concentrations, resulting in temporary inactivation of neurons preventing continuing recruitment [17]. Experiments using DC fields applied parallel to the neuronal axis demonstrated that the resulting neuronal depolarization also suppressed epileptiform discharges in different models [6,18]. The concept of local closed-loop modulation of electric fields has been successfully transferred to human studies [19].

Remote

Direct effects of remote HFS on cell bodies in the target area have been verified by single-unit recordings [20]. Activation of direct axonal connections between the subthalamic nucleus (STN) and the frontal cortex may be one possible antiepileptic mechanism of STN DBS [21]. However, there is increasing evidence that the effect of DBS on the basal ganglia for Parkinson's therapy is not sufficiently explained by functional ablation, but more convincingly by network-wide modulating effects [22]. It is possible that the same applies to remote stimulation of the epileptogenic zone. In addition, long-term potentiation may also be important.

Brain stimulation at different targets: *in vivo* experience

■ Local stimulation

Local open-loop pulsatile stimulation: hippocampus & amygdala

Low frequency

Several animal studies investigated the antiepileptic effect of LFS [7,23–27]. Administration of 1–10 Hz LFS led to a significant increase in after-discharge threshold [25,27] or a decrease in after-discharge duration [24]. Other investigations demonstrated this effect was actually related to the co-administration of a low-level DC current; a phenomenon known as 'quenching' [23].

High frequency

More evidence exists for HFS of the mesial-temporal structures. Subacute hippocampal stimulation for 2–3 weeks abolished clinical seizures and reduced interictal discharges after 5–6 days in seven patients [28]. Boon *et al.* studied ten patients with chronic continuous open-loop HFS (130 Hz) of the mesial-temporal structures, with a mean follow-up of 31 months. Patients were implanted during intracranial EEG evaluations for intractable nonlesional temporal-lobe epilepsy (or incongruent noninvasive testing), and had to demonstrate a greater than 50% reduction in interictal discharges over a 7-day trial period. Nine patients had unilateral stimulation and one patient (with bilateral-independent ictal onsets) had bilateral stimulation. One patient had a greater than 90% reduction of mean monthly seizures over 6 months compared with baseline, five had a greater than 50% reduction, with the other five patients having less than a 50% reduction, including one 'nonresponder' [29]. Velasco *et al.* studied nine patients with hippocampal chronic open-loop stimulation using similar settings (frequency of 130 Hz) and found a greater than 95% seizure reduction in five patients with normal MRIs and a 50–70% reduction in patients with hippocampal sclerosis at 18-month follow-up. Seizure reduction began earlier in the normal MRI group (2 vs 8 months). Velasco *et al.* postulated that either a more intact neuronal network is required for stimulation to be effective or that scar tissue in hippocampal sclerosis causes higher tissue impedence [30]. Another double-blind multiple crossover trial of four patients with left hippocampal stimulation (190 Hz frequency and 90 µs pulse width), with 1 month on 1 month off cyclically over 6 months, demonstrated a median 15% seizure reduction [31]. A randomized controlled trial of electrical stimulation of the hippocampus versus traditional surgery for intractable temporal-lobe epilepsy with mesial-temporal sclerosis on MRI is underway (CoRaStiR) [201]. In addition, a randomized controlled trial of unilateral hippocampal stimulation versus medical therapy is also recruiting patients (METTLE) [202].

Local closed-loop high-frequency pulsatile stimulation: RNS

The only large-scale randomized clinical trial of closed-loop (responsive) stimulation is the RNS® System Pivotal Clinical Investigation (NeuroPace, Inc., Mountain View, CA, USA). The RNS System involves several components. Up to four subdural strips or depth electrodes, each with four contacts, are placed intracranially at the seizure focus. Only two can be connected at a time, with the extra leads available for the future in case the initial choices are ineffective.

The leads are then attached to the neurostimulator, which contains a battery and computer processor, and is placed into the skull (FIGURE 1). Repeat surgery for a battery change or switching of electrode contacts only requires a skin incision, without entering the skull or dura.

In addition to detecting and stimulating, the neurostimulator has a small amount of data storage for several minutes of raw corticography. The neurostimulator collects and stores statistical information on the types of detections and stimulations over time. Patients are sent home with a data transmitter wand attached to a laptop computer and are instructed to download data at least once a day. Data are then transmitted from the laptop, via the internet to a secured data respository, and are made available to the investigators on a secure website.

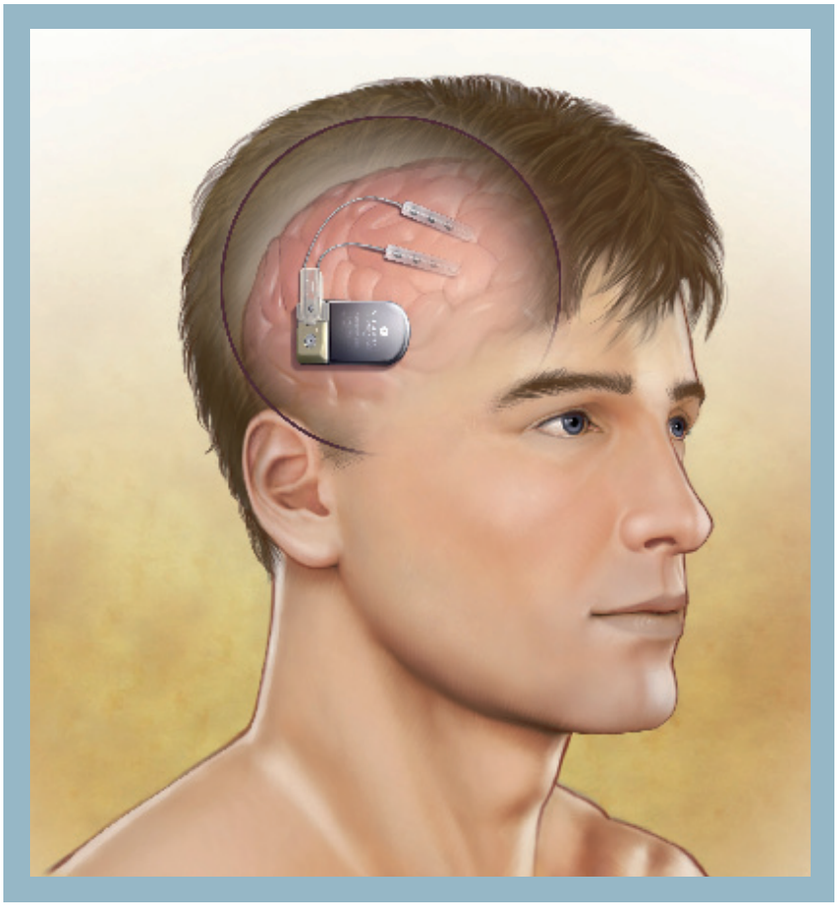

Figure 1. Neuropace RNS® System *in situ*. This system is not currently approved by the US FDA.
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Once seizures have been recorded, the investigator uses software to tune the detectors to the patient's individual EEG patterns. Further adjustments over time may improve detection sensitivity and specificity. Stimulation parameters include voltage, pulse width, frequency, and both mono- and bi-polar stimulation are available.

In 1999, Lesser *et al.* reported that brief pulse stimulation was found to terminate afterdischarges caused by focal cortical stimulation during the mapping stage of two-stage epilepsy surgery in humans [32]. Subsequently, the RNS System was developed and evaluated in several clinical trials. Initial studies involved small numbers of patients undergoing intracranial EEG monitoring for epilepsy surgery, and tested both the seizure detection algorithms and an external stimulator [33]. Next, a trial was performed in 65 patients, primarily assessing safety but also exploring efficacy [34]. The success of this trial led to a larger, randomized, multicenter double-blinded pivotal trial to establish efficacy. The blinded evaluation period for this study was completed in late 2009 and results were reported in abstract form [35].

In the pivotal trial, there were 191 patients with intractable partial epilepsy who were implanted with the neurostimulator after a 3-month baseline period. Patients with vagus-nerve stimulators had them turned off for 3 months before enrollment into the baseline period. After surgery, the neurostimulator recorded seizures but no responsive stimulation was given for the first month. This allowed investigators to begin tailoring the seizure-detection algorithm to each patient's patterns. The randomized, blinded phase began with 1 month of stimulation titration followed by a 3-month phase for comparison to the baseline. Half of the patients received stimulation in the blinded phase, and all received stimulation thereafter. Long-term data were available for 171 subjects. During the blinded phase, the subjects who were randomized to receive responsive stimulation experienced a significantly greater reduction in seizures (37.9%) compared with the subjects randomized to receive no stimulation (17.3%), $p = 0.012$ (p-value and reduction in seizure frequency estimated using the generalized estimating equations method). In the open-label phase with longer follow-up, the 50% responder rate was 47% for the last 12 weeks of data, compared with the baseline. The RNS System study is not directly comparable to a drug study with fixed dosing, as the investigators were allowed to continually adjust detection and stimulation parameters. Given this flexibility, it is perhaps not surprising that the long-term results were better than the blinded phase. There is also the possibility that stimulation has long-term effects as seen in VNS, so that only a longer follow-up will show maximal improvement. Antiepileptic drug changes were allowed in the open-label phase, but the data on this are not yet available, making it hard to assess its impact. Full assessment of responsive stimulation will await final publication of detailed data.

Local DC stimulation

In vitro and *in vivo* animal studies in rats suggest that local DC stimulation can modulate epileptiform activity by causing neuronal depolarization [7,18]. However, the disadvantages of DC stimulation, including electrode erosion, rebound excitation, and dependency on the angle between the electric field and the neuronal axis, limit its practical use and interest has waned. In addition, an intensity-related increase of after-discharge and seizure threshold can occur either accidentally by low-level DC leakage of some stimulators or by the co-administration of a positive DC current (1–15 µA) for 15 min following the kindling stimulation (a 'quenching' effect that can last for up to 1 month after stimulation) [23].

Transcranial magnetic stimulation

Transcranial magnetic stimulation (TMS) uses magnetic fields to noninvasively induce electric currents in the brain. TMS is more often used as a diagnostic tool to evaluate local cortical function. During diagnostic use, single-pulse TMS has been demonstrated to increase interictal spikes or even induce seizures in susceptible patients [36,37]. However, repetitive TMS can produce lasting cortical inhibition. Uncontrolled studies found a reduction in interictal discharges and a reduction in seizures over focal epileptogenic lesions [38]. A placebo-controlled trial with 24 patients used 1-Hz TMS for 15 min twice a day and found no significant benefit over 8 weeks [39]. Other results have been similarly disappointing [40–44]. Patients with well-localized cortical dysplastic lesions have done better in clinical studies [45]. Side effects include headache and seizures (occurring in ~1.4% of patients).

Remote stimulation

Remote closed-loop HFS: DBS

Limited animal and human data exist that demonstrate suppression of cortical epileptiform activity by remote closed-loop stimulation of the

caudate [46,47]; remote studies have focused on open-loop stimulation. Magnet use for seizures in the VNS setting constitutes a form of remote closed-loop therapy.

Remote open-loop HFS: DBS

Deep-brain stimulation involves the stereotactic placement of DBS leads within deep neuronal structures that are then tunneled subcutaneously to a stimulator device (usually in the upper chest area). Different forms of DBS for epilepsy will be discussed by neuronal target site.

STN & substantia nigra pars reticularis

Stimulation of the STN and the substantia nigra pars reticularis (SNpr) are based on the concept of the nigral control of epilepsy system [48,49]. Suppression of the tonically firing SNpr resulted in activation of the dorsal-midbrain anticonvulsant zone located in the superior colliculi [50]. The STN keeps the SNpr active and, thus, blocks the dorsal-midbrain anticonvulsant zone. In turn, inhibition of the STN inactivates the SNpr and, consequently, activates the dorsal-midbrain anticonvulsant zone. In addition, more recent data demonstrated that HFS (130 Hz) of the STN increases glutamate concentrations in the globus pallidus and SNpr, and increases γ-aminobutyric acid in the SNpr [51], as well as causing antidromic activation of corticosubthalamic connections [21,52]. Animal studies of SNpr stimulation [53] demonstrated only modest effect [54], and one showed aggravation of seizures with repeated stimulation despite defining optimal parameters from single stimulation (60 Hz) [55].

In animals, bilateral STN stimulation has been demonstrated to lower the seizure threshold and, in generalized epilepsy models, has suppressed seizures [9,56]. In a kainic acid model, bilateral STN stimulation reduced the total seizure activity duration in the first 60 min by 32% [57] and the generalized seizure activity duration by 78% [58].

In human patients, data are only available from small uncontrolled case series of 14 patients. The seizure-reduction frequency ranged from 0% to 88% [59–61]. One report indicated a greater than 50% reduction in myoclonic seizures and improvement in mobility with bilateral monopolar HFS of the STN in a patient with progressive myoclonic epilepsy [62]. Open-loop HFS of the STN or SNpr may reduce seizure threshold, frequency and duration. However, the effect is, in general, modest, and there are no explanations available as to why some patients benefit more than others. A double-blind crossover multicenter study is underway – STN/SNpr Stimulation For Ring Chromosome 20 Epilepsy (STIMEP).

Caudate nucleus

Early animal studies demonstrated that interictal stimulation of the caudate nucleus (CN) produced epileptiform discharges, which could trigger seizures and could even enhance seizure discharges [63].

More recent animal experiments demonstrated cessation of epileptic activity during interictal low-frequency caudate stimulation. However, the interruption of interictal epileptiform activity was frequently followed by an electroclinical seizure immediately after the end of the stimulation, which was interpreted as an expression of postinhibitory rebound [64]. Modulation of stimulation could overcome this effect. High-frequency caudate stimulation [65], continuous, as opposed to alternating, stimulation [66] and alteration of stimulus duration [67] reduced hippocampal interictal discharges. Few studies in humans are available [68]. LFS resulted in a significant decrease in interictal epileptiform activity, and in a cessation of ictal epileptic discharges in the amygdala nucleus and in the hippocampal gyrus. HFS in practically any part of the CN led to augmentation of epileptiform activity [69]. The same group demonstrated that interictal unilateral LFS of CN suppresses bilateral focal discharges from the contralateral temporal regions. Inhibitory effects were more likely with stimulation of the ventral versus the dorsal part of the CN. By contrast, HFS of both the dorsal and ventral parts of the CN enhanced epileptiform activity in the ipsilateral hemisphere. The authors hypothesize a frequency-related preferential activation of the different neuronal systems of the CN [70].

Anterior thalamus

The anterior thalamus (ANT) has direct cortical connections and plays an important role in the limbic system as a relay station within the circuit of Papez. Animal studies indicate an increased seizure threshold [71] and time delay of EEG seizure onset after pentylenetetrazol injection [72] during ANT stimulation. However, in the kainic acid model, a different stimulation setting was associated with an increase in seizure frequency, often at the onset of stimulation [73].

The first human study using ANT stimulation demonstrated a decrease in seizure frequency in four out of six stimulated patients [74].

Subsequently, several open-label studies, using remote open-loop stimulation and including up to five patients, demonstrated a reduction in seizure frequency between 40 and 50% in patients with focal and generalized epilepsies, sustained for over 5 years [75–79]. Part of the positive effect might be related to the microthalamotomy during implantation [75,80]. Remote closed-loop HFS targeting the anterior thalamic nucleus in four patients with bitemporal-lobe epilepsy, using automated seizure detection algorithms, demonstrated a reduction in seizure frequency of 40.8% [81,82]. The same group also demonstrated a reduction in seizure frequency of 75.6% (range: 53–92%) using a high frequency, 175 Hz, periodic, round-the-clock stimulation paradigm in patients with bitemporal-lobe epilepsy [81].

In 2010, a multicenter randomized double-blind prospective trial of bilateral anterior nuclei of the thalamus stimulation, for localization-related epilepsy was reported [83]. The study used the Medtronic Kinetra® DBS device (Medtronic, Minneapolis, MN, USA) (Figure 2). The trial included 110 participants using a stimulation protocol of 5 V, 90 µs pulse width, 1 min 'on' and 5 min 'off', and a stimulus frequency of 145 Hz. At the end of the first 3 months (the double-blind phase), the stimulated group had a 29% greater seizure reduction compared with the control group (p = 0.002). After 2 years of open-label stimulation, there was a 56% median decrease in seizures and 54% of patients had at least 50% seizure reduction. Device-related paresthesias was the most common adverse effect, seen in 18.2% of patients. Additional side effects included asymptomatic hemorrhage in 4.5%, and infection of the stimulator pocket in 7.3%, of the stimulator lead in 5.5% and at the burr hole site in 1.8%. Two patients had stimulus-linked seizures when stimulation was initiated that subsided with lower voltage. Three cases of sudden unexplained death in epilepsy, one traumatic death and one suicide were encountered, but were concluded to be unrelated to the device. Of note, significant seizure reduction was only seen in patients with temporal-lobe epilepsy (44.2%, n = 33 vs 21.8%, n = 29 in the control group; p = 0.025). Patients with extratemporal-lobe focal or multifocal epilepsies failed to demonstrate a significant benefit.

Figure 2. Medtronic's Activa® PC device for deep-brain stimulation. This device is not currently approved by the US FDA for the treatment of epilepsy.
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Centromedian thalamic nucleus & mammillary bodies

Animal data from stimulation at other targets with close connections to the ANT, such as the mammillary nuclei, also indicate the production of a higher seizure threshold [84]. A human trial, including three patients, has been initiated but only safety and no efficacy data have been published [85].

The centromedian thalamic nucleus is part of the reticular activating system and, owing to its location, is an easy target for stereotactic neurosurgery. Stimulation of the centromedian thalamic nucleus at 3–6 Hz produces high-amplitude spike and wave complexes that resemble seizure patterns seen during typical 3-Hz spike and wave complexes in generalized seizures, whereas stimulation at 60 Hz produced desynchronization [10]. The first case series of centromedian thalamic nucleus stimulation in five patients with generalized epilepsy reported reduced seizure frequency lasting for several months compared with baseline [86]. In a larger series of 13 patients by the same group, 90% seizure frequency reduction was reported in patients with generalized tonic–clonic seizures and absence seizures, whereas no effect was seen in patients with focal epilepsies [87]. Fisher *et al.* tried to replicate these uncontrolled results with a placebo-controlled study [88]. However, they found only a 30% seizure frequency reduction compared with baseline during 3 months of stimulation, and only 8% seizure frequency

reduction during a 3-month 'wash out' period after the stimulation. After 6 months, the study was continued as an open-label trial, during which some stimulated patients reported up to 50% seizure reduction.

Locus cereulus/trigeminal nerve

A reduction of seizures was noted in two patients with epilepsy implanted with unilateral stimulators "in the vicinity of the locus cereulus" in the 1970s [89]. Stimulation parameters employed were a pulse width of 120 µs (biphasic), a frequency of 40–60 Hz and variable on/off times [89]. Trigeminal-nerve stimulation for epilepsy by one group attempted to indirectly modulate afferent pathways through the locus cereulus and nucleus tractus solitarius [90,91]. A rat model demonstrated that chronic stimulation of the infraorbital nerve reduced seizures by 87%. The effect was more pronounced when bilateral stimulation was used and when a closed-loop paradigm of seizure detection was followed by 333 Hz stimulation [92]. However, careful analysis of the rat EEG data of this experiment suggests that the EEG activity might not resemble seizure activity but merely unspecific patterns of drowsiness, with the sensory stimulus resulting in an arousal. A pilot study in humans demonstrated that four of seven patients had a 50% reduction in seizures after 3 months of stimulation [93]. An uncontrolled human trial of open-loop remote trigeminal stimulation of 13 patients showed a mean seizure reduction of 59% at 12 months. One patient had a greater than 90% reduction and five patients had over 50% reduction in seizures. The protocol consisted of ophthalmic electrodes, less than 30 s on and less than 30 s off, for 12–24 h/day, at 120 Hz and 250 µs. Side effects included tingling, headache and skin irritation [94].

Other remote targets

Reports of DBS for epilepsy in other targets, such as the posterior hypothalamus, corpus callosum, zona incerta and mammillothalamic tract, exist [95–98].

Remote open-loop HFS: VNS

VNS Therapy® (Cyberonics, Inc, Houston, TX, USA) is a device placed in the subcutaneous tissue of the upper chest, with leads that track to the vagus-nerve in the neck (Figure 3). Intermittent remote open-loop stimulation and remote closed-loop stimulation (by way of an activating magnet in response to seizures) account for its effect.

Figure 3. Cyberonic's VNS Therapy® pulse model 102 and demipulse™ model 103.
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Interest in VNS expanded following animal studies in cats that demonstrated suppression of interictal spiking [99] and EEG desynchronization [100]. The first human patient, implanted in 1988 by Penry, became seizure free [101]. The first randomized controlled study was performed in 1992 and was followed by five more studies that led to FDA approval of the device in July 1997.

The exact mechanism of VNS in humans is unknown. An alternating synchronization followed by more prominent desynchronization of EEG may be a potential mechanism for the action of VNS [102]. Other studies have found decreases in excitatory neurotransmitters (aspartate) and increases in γ-aminobutyric acid, associated with seizure reduction [103,104]. Functional imaging demonstrated activation or deactivation of the thalami, subcortical structures, cingulated gyrus, temporal neocortex and mesial-temporal structures [105–111].

Stimulation paradigms for VNS

The FDA recommended stimulation frequencies between 20 and 30 Hz. Lower-frequency stimulation at 5 Hz is associated with reduced brain stimulation [112] and may facilitate stimulation of slow-conducting C-fibers, and led to increased side effects [113]. Stimulation frequencies of 50 Hz and higher may result in irreversible vagal-nerve fiber damage [114].

Intensity currents between 0.8 and 2 mA are considered effective [113]. Stimulation can be increased incrementally by 0.25 mA – usually every 1–2 weeks. Stimulation-induced side effects may increase with rising current delivery (either increased intensity or widened pulse width). The threshold current is higher in young children, indicating that a higher current or larger pulse width is required in order to achieve equivalent effects [115].

The usual pulse-width settings include 500 and 250 µs. Increase of the pulse-width leads to increased delivery of current, although this increase is not linear [113].

Standard stimulation intervals consist of a 30 s on and a 5 min off period. Duty cycles should not exceed 50% of the complete stimulation paradigm in order to prevent nerve injury [114]. Some VNS-resistant patients may experience better seizure control with faster cycles [116].

Efficacy of VNS

Two randomized double-blind placebo-controlled multicenter trials (E03 and E05) of VNS in epilepsy included a total of 313 patients older than 12 years of age with predominantly partial seizures [117–119]. Both of these trials compared two VNS stimulation paradigms, 'high' versus 'low' ('control') stimulation. Seizure frequency reduction in the E03 and E05 trials was 24.5% ($p < 0.01$) and 28% ($p < 0.05$) in the high-stimulation group versus 6.1 and 15% in the low-stimulation group ($p < 0.01$). Secondary outcomes in the E03 trial showed that 31% had a seizure reduction of over 50% in the high-stimulation group compared with 13% in the low-stimulation group ($p < 0.05$).

Limitations exist with these trial designs as the active control group was also exposed to stimulation, and participants or physicians may have been able to detect current delivery in the treatment arm owing to possible stimulation-related side effects. Unblinding may also have resulted from lack of perceived VNS output after handheld magnet activation in the control group. There are no randomized controlled data related to long-term VNS use.

Open-label, nonblinded, longer-term studies indicate that VNS treatment efficacy seems to further improve during follow-up. George *et al.* reported that 26 of the 31 patients initially randomized to high-frequency VNS had a 52.0% seizure frequency reduction up to 18 months after completion of the E03 trial [120].

The XE5 trial (long-term prospective efficacy and safety study after E05) showed that the median seizure frequency reduction was 45% [121]. An analysis suggested that the increased efficacy was not related to changes in stimulation parameters [116]. Selection bias is a limitation in long-term studies, as patients who have a poor response to stimulation tend to exit early, leaving only patients who have a relatively good response to stimulation during longer follow-up periods.

Vagus-nerve stimulation has demonstrated some effect in pediatric patients with partial seizures [122,123], epileptic encephalopathies [124], Lennox–Gastaut syndrome [125], tuberous sclerosis [126], hypothalamic hamartomas [127] and Landau–Kleffner syndrome [128].

In a series of patients over 50 years of age, 21 out of 31 had a 50% or greater decrease in seizure frequency and improved quality of life scores after 1 year [129].

Level-one evidence supports the use of VNS in patients with partial seizures [119]. A third of patients experience seizure reduction of at least 50% [130], and similar results have been observed in adults and children, with additional improvement after longer stimulation duration [131]. The observation of positive VNS effects on mood, alertness and quality of life has ignited interest, and there are ongoing studies of VNS in other clinical areas such as depression and mood disorders [132], migraines [133], and conditions with memory difficulties and impaired alertness [134].

Remote open-loop HFS: cerebellum

Evidence that electrical stimulation of the cerebellum had an inhibitory influence on other brain structures has existed since the late 18th century [135,136]. The first human cerebellar stimulators were placed by Cooper in the 1970s. In his uncontrolled series, 56% of patients "responded well" [137], but electrode placement and stimulation parameters were highly variable [138]. Further uncontrolled studies reported that 60% of patients became seizure free and 20% had reduced seizures [139] at stimulation frequencies of 150–200 Hz.

However, two controlled double-blinded trials (using a sham cerebellar stimulator with aluminum foil blocking the radiofrequency transmitter) demonstrated no statistical benefit [140,141].

In several series, patients or families reported increased alertness, improved ability to concentrate and improved mood [137,140,141]. Reduction in anxiety, depression and tension, as well as improved control of aggression, was proposed to be secondary to cerebellar influences on the reticular system [142]. The early cerebellar stimulators were also limited by poor reliability of the radiofrequency stimulators, lack of consensus on the optimal placement sites and stimulation settings, and lack of objective measurements in the only controlled clinical trials [143].

Interest in cerebellar stimulation was renewed in 2005, with a randomized controlled trial of bilateral superomedial cerebellar stimulation involving five patients. There was a 3-month blinded period 1 month after implantation. A

total of three of the five patients had stimulation turned on, while the other two had stimulation turned off. This was followed by an open-label phase with follow-up between 10 months and 4 years [144]. A reduction of seizures by 33% was seen in the 'on' group compared with 93% in the 'off' group (p = 0.023). The mean seizure reduction in the open-label phase was 41% from baseline at 6 months. Four patients required further surgery for infection or electrode adjustment. The low numbers of subjects and high rate of reoperation for complications has led to some skepticism [145].

Problems with electrical brain stimulation in patients with epilepsy

Seizure induction & kindling

The kindling phenomenon is a concern in chronic electrical brain stimulation; a proconvulsant effect that outlasts the electrical stimulus [146,147]. Repeated alternating current HFS of the brain is used as a widely accepted experimental epilepsy model [148]. HFS of the amygdala, the hippocampus and neocortical structures has been demonstrated to facilitate synaptic transmission that may ultimately induce epilepsy [149]. In addition, proconvulsive effects in animals have been demonstrated for HFS (800 Hz) in the STN [9], LFS (8 Hz) in the ANT and caudate [71], and, in humans, proconvulsive effects have been shown for LFS in the ventral centromedian nucleus [150,151]. Currently, there is no evidence that human electrical brain stimulation is able to induce secondary epileptogenesis [152]. However, the pro-epileptogenic implications of kindling on humans have not been systematically investigated yet. Among the large number of patients with chronic DBS for reasons other then epilepsy, only two case studies reported on the development of epilepsy following thalamic stimulation for chronic pain [153,154].

Side effects

Deep-brain stimulation

Information regarding the side effects of DBS derives mainly from studies on movement disorders. A careful selection of appropriate patients seems to be the most important presurgical aspect to avoid later complications [155].

Deep-brain stimulation requires a craniotomy and needles passing through the brain with the risk of intracranial hemorrhage and lesion of adjacent tissue [155,156]. An autopsy of a patient who died from sudden unexpected death in epilepsy while in the anterior thalamic stimulation trial demonstrated only a mild local tissue reaction at the lead site [157]. Infection, edema, cerebrospinal fluid leak, increased intracranial pressure, confusion and seizures have been reported [137,155,156,158]. Postoperative hardware-related complications, including infection, delayed hematoma, skin erosion or scarring ('bowstringing'), electrode fracture, electrode dislocation, and hardware failure vary between 6.7 and 49% in the literature [158–163].

Adverse events, related to the stimulated target and its adjacent tissues, are mainly adjustable but at the cost of decreased efficacy [156]. Depending on the stimulated target, paresthesias, muscular cramp, dystonia, dyskinesias, dizziness, nystagmus, dysarthria, gait and balance disturbances, ataxia, impaired proprioception, weight gain, and psychiatric adverse effects have been reported [156,158]. Stimulation of mesial-temporal structures have not yet reported behavioral emotional changes [28,29] or neuropsychological deficits [30].

A recent review of the literature revealed that overall complication rates in DBS can exceed 25%, and persistent neurologic deficits associated with DBS occur in 4–6% of cases [164]. Events of death related to DBS device implantation have been reported [165]. However, the estimated risk for mortality in patients with uncontrolled seizures is 0.5% per year, and is cumulative [166].

Responsive neurostimulation

Safety was comparable to that of acute intracranial EEG for surgical localization, and to chronic DBS for movement disorders. No unexpected adverse events occurred, and there was no difference between the stimulated and sham groups in adverse events, suggesting that the main risks of the procedure relate to the surgery and presence of the implant itself rather than the stimulation [34,35].

Vagus-nerve stimulation

Infections occur in 3–6% of patients [167,168]. In the E05 trial, 1.5% of patients required device explantation owing to infection [122]. A recent study reported hardware failure in 2.7% of 74 patients, with a minimum follow-up of 1 year [168]. Vocal-cord paralysis and dysfunction can occur as a result of the surgery itself and/or as a result of the stimulation [117,122,169]. Postoperative vocal-cord paralysis is often temporary and patients may recover as swelling improves [170].

Vagus-nerve stimulation can lead to improvement of behavioral problems and has mood-stabilizing effects [125,171,172]. Nevertheless, acute psychosis and depression have been described after VNS insertion [173].

Dyspnea can be caused by adduction of the left vocal cord, which results from intensity-dependent stimulation of the recurrent laryngeal nerve [174]. Snoring, sleep apnea and gasping during sleep have been reported [175], in some cases to a greater degree with rapid cycling [176]. Occasionally, aspiration during VNS has been observed in children with severe pre-existing mental and motor disabilities [177].

Cardiac asystole is a rare complication during the testing of the vagus-nerve stimulator at the time of implantation, with an estimated frequency of one in 875 (0.1%) [178,179]. No major autonomic effects on heart rate variability were described with chronic VNS [180], although two cases of 'late asystole' have been reported [181]. Implantation of the metal stimulator limits future MRI scanning owing to possible diathermy effects and manipulation of stimulator settings by the magnetic field. Battery life is less of a concern with newer models such as the Demipulse™ 103 (**Figure 3**).

Future perspective

Electrical brain stimulation is a promising alternative technique in the treatment of medically refractory epilepsy in patients that do not qualify for resective epilepsy surgery. The mechanisms of action are still poorly understood. It is not clear how much efficacy depends on lobar localization, the precision of electrode placement on the focus or the underlying pathology. Does stimulation need to affect all or part of the ictal onset zone, or the interictal irritative zone (a phenomenom also known as the overdrive concept)? Does stimulation of another part of an epileptogenic network, distant from the ictal onset zone, affect seizure control? What stimulation parameters are most effective, and do they vary by location, pathology or even just from one individual to another? Can we move from seizure detection algorithms to seizure prediction (even by seconds or minutes) and improve efficacy? Do different medications enhance or inhibit the effects of stimulation? Improving our knowledge of neuronal networks in patients with epilepsy may allow a better understanding of how to apply electrical brain stimulation in each case.

Therefore, clearer indications and ideal stimulation parameters for electrical brain stimulation in different seizure types and syndromes need to be defined. Identification of the best candidates is critical for success. There are no studies providing head-to-head comparisons of established AEDs and limited randomized double-blind data exist for children, the elderly and individuals with generalized epilepsies. There is evidence that electrical brain stimulation is cost effective over time [182], given that the target population of patients with intractable epilepsy make up the majority of the economic cost of epilepsy [183].

The wealth of data from chronic intracranial recordings from RNS systems open new avenues for understanding epilepsy. Some small studies have already confirmed catamenial seizure fluctuations [184] and other biorhythms affecting seizures may become evident. Being able to record chronic EEG may allow hyperacute trials of new drugs and improve screening for new treatments. We may begin to assess the relationship of epileptiform activity to cognitive and emotional fluctuations. We may see seizures unknown to the patient, which might lead to ethical issues regarding driving permission in patients who report clinical seizure freedom.

The treatment is potentially reversible and adjustable as opposed to resective epilepsy surgery; however, the treatment is still palliative and cannot yet cure epilepsy. Further technical development may improve devices and lead to longer battery life. Most studies have been uncontrolled trials but the recent expansion in controlled trials, encouraged by the success of VNS for epilepsy and DBS for movement disorders, may provide additional information. Chronic open-loop thalamic or hippocampal stimulation, and closed-loop local stimulation seem to hold the most promise. Two devices (the NeuroPace RNS System and Medtronic's Activa® DBS) are in the process of being submitted to the FDA and may enter clinical practice in the near future. More prospective human randomized controlled trials are needed.

Financial & competing interests disclosure

E Geller and P Widdess-Walsh are investigators in the Neuropace RNS® System pivotal trial. P Widdess-Walsh is on the speakers bureau of UCB and GlaxoSmithKline. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Executive summary

- A large body of evidence, including laboratory, animal studies and human trials, support the efficacy of electrical brain stimulation to reduce seizures.
- Although a surgical procedure is required for implantation, the safety and tolerability of these devices is reasonable, while risk of continuing uncontrolled seizures is high.
- A variety of devices have been used in epilepsy, with different neuronal targets (either 'local' or 'remote'), with either open-loop (continuous) or closed-loop (responsive) stimulation.
- Vagus-nerve stimulation has been approved by the US FDA since 1997 and can reduce seizures by 50% in 30% of patients with partial epilepsy.
- Reported results of randomized controlled trials of deep-brain stimulation of the anterior thalamus and local responsive neurostimulation are encouraging, are pending FDA approval and may move into mainstream practice in the near future.
- Randomized controlled trials of hippocampal stimulation are underway and results are highly anticipated.
- Further research and greater insight into mechanisms of action and optimal stimulus parameters of electrical brain stimulation in epilepsy should allow enhanced efficacy in specific seizure types and syndromes.

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