Neurostimulation, neuromodulation, and the treatment of epilepsies

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SUMMARY

Introduction. Neurostimulation and neuromodulation are techniques that may be able to affect the course of epilepsy. In the last 20 years, since the approval of VNS, we have observed a surge of studies assessing the potential of other devices and techniques for the treatment of pharmacoresistant epilepsies including deep brain stimulation (DBS), responsive neurostimulation (RNS), trigeminal nerve stimulation (TNS), transcranial direct current stimulation (tDCS), and repetitive transcranial magnetic stimulation (rTMS). Are these devices and techniques simply another treatment option that can be offered to patients with epilepsy or do they offer specific advantages when compared to the standard antiepileptic drugs (AEDs)?

Aim. The aim of this review is to present the neurostimulation and neuromodulation devices and techniques that are now in use, or at least available for testing and to discuss the science behind them, their applications, efficacy, potential risks vs. benefits and, above all, how to navigate the choices so clinicians are able to provide their patients with the best possible option for the treatment of epilepsy.

Material and methods. We analyzed PubMed and MEDLINE databases to select the most salient and recent (up to November 2014) publications on each treatment device. In addition to these searches bibliographies of selected articles were hand-searched for possible sources.

Discussion and conclusions. Great progress in neurostimulation and neuromodulation has been made over the last two decades with 2 devices (VNS, RNS) approved for the treatment of epilepsy in the US and three (DBS in addition to VNS and RNS) in Europe. The future of neuromodulation/neurostimulation is exciting – various studies and efforts are underway and will provide us with more data in the future. There appears to be one clear advantage of these treatments/devices over the AEDs that is consistently noted – routinely observed is continuous improvement in seizure control over time. This is something that the AEDs have thus far failed to deliver.

Key words: neurostimulation • neuromodulation • epilepsy • VNS • DBS • RNS • TMS • TNS

INTRODUCTION

Epilepsy is one of the most common neurological diseases affecting 1% of the population or approximately 65 million people worldwide (Thurman et al., 2011).

Previous studies have shown that between 20% and 40% of patients with epilepsy have refractory, or drug-resistant, epilepsy meaning that they continue to have

seizures despite treatment with at least two appropriate anti-epileptic drugs (AEDs) (Annegers et al., 1979; Cockerell et al., 1995; Kwan and Brodie, 2000; Kwan et al., 2010 Callaghan et al., 2011). As a result of the continued seizures, patients with medication-resistant epilepsy have poorer quality of life than medication-controlled patients (Jacoby et al., 1996). Quality of life in these patients is also affected by the increased presence of negative mood states, particularly depression, and adverse medication side effects (Boylan et al., 2004; Szaflarski et al., 2006). To improve seizure control, the quality of life, and mood in patients with intractable epilepsy treatment plans need to expand beyond the use of AEDs and offer treatments that have different mechanisms of action and side effect profiles.

When AEDs fail to manage patient's seizures, the next course of action is to assess the patient's candidacy for surgery. In patients with refractory temporal lobe epilepsies, the most effective surgical treatment involves the removal of the epileptogenic focus (Wiebe et al., 2001). While this form of surgical treatment can control or dramatically reduce seizures and improve quality of life, patients with generalized epilepsies and/or patients with focal forms of epilepsy that do not allow for the localization of an epileptogenic area are typically not candidates for surgery. When pharmaceutical and surgical treatment plans are ineffective or not a viable option, neurostimulation and neuromodulation techniques could be considered as a means for controlling or reducing seizure burden and improving the quality of life in patients with refractory to treatment epilepsies. While the end-effects of neuromodulation and neurostimulation are similar – changes in cortical excitability – the proposed mechanisms of action are likely different. Neurostimulation techniques e.g., transcranial magnetic stimulation (TMS) allow for both, neurostimulation and neuromodulation while transcranial Direct Current Stimulation (tDCS) is purely a neuromodulation technique. In TMS, a depolarization of the cellular membrane by electromagnetic induction is expected, resulting in modification of cortical excitability that may extend beyond the stimulation itself as it is observed with rTMS. On the other hand, in the neuromodulation techniques such as tDCS, the current penetrates the skull and enters the brain to modify membrane potentials but not to depolarize the cells. These devices and techniques act by targeting a specific neuronal region or circuit to modulate the neuronal activity in the specified area and to create sustained but ad-

justable and reversible changes in the patient's symptoms (Fisher and Velasco, 2014). In this review, we will focus on the mechanisms of action, efficacy, and potential drawbacks of several neurostimulation and neuromodulation techniques including vagus nerve stimulation (VNS), responsive neurostimulation (RNS), deep brain stimulation (DBS), trigeminal nerve stimulation (TNS), tDCS, and rTMS.

AIM

The aim of this study is to discuss the most prominent neurostimulation and neuromodulation devices and techniques that are now in use, or at least available for testing, in patients with epilepsy. We will discuss the evidence for efficacy, mechanisms of action, and applications of each device/technique.

METHODS

We analyzed PubMed and MEDLINE databases to select the most salient and recent (up to 2014) publications on each treatment device. In addition to these searches bibliographies of selected articles were hand-searched for possible sources.

REVIEW AND DISCUSSION

Vagus Nerve Stimulation (VNS)

The trial-based use of VNS for the treatment of epilepsy in humans began in 1988 with the official approval for the treatment for epilepsy in 1994 in Europe and in 1997 in the United States and Canada (Hassan and Al-Quliti, 2014). The guideline recently published by the American Academy of Neurology (AAN) indicates that VNS may be considered, in addition to standard indications, for the treatment of epilepsy in children, patients with Lennox-Gastaut Syndrome (LGS) and for improving mood in patients with epilepsy (all Level C recommendations) (Morris et al., 2013). The only currently approved FDA device was developed by NeuroCybernetic (Cyberonics Inc., Houston, TX, USE); it uses a prosthesis that is typically anchored underneath the skin of the upper left chest to deliver stimulation (Ben-Menachem, 2012). The VNS device has a flexible bipolar lead attached to it that is placed on the peripheral vagus nerve located in the neck. The electronic generator in the prosthesis is externally programmed to deliver stimulations that travel through the lead to the vagus nerve. This is an open-loop system that typically delivers stimuli throughout the day and night at

30 Hz for 30 second "on" periods, which are separated by 3–5 minute "off" periods (DeGiorgio and Krahl, 2013). These parameters can be modified including changes to what is called "rapid cycling" or "heavy duty cycling" with shorter on and off parameters (Gurbani et al., 2004). VNS can also be used as a closed-loop system in response to an aura or partial seizure by activating it with a hand-held magnet, but this approach is useful in only 30–40% of patients (Boon et al., 2002; Vonck et al., 2005). Due to the structure of the vagus nerve, unilateral stimulation produces equally effective afferent responses bilaterally, but right-sided VNS can produce bradycardia so left side VNS is preferred in clinical practice (Saper et al., 1990; Hassan and Al-Quliti, 2014). Depending on the settings used, the battery life for the VNS system usually ranges from 8–12 years, at which point the generator must be replaced (Ben-Menachem, 2012).

Mechanism of Action
The vagus nerve plays a role in the autonomic parasympathetic control of the heart and digestive tract, as well as in the conveyance of sensory information regarding various internal organs to the central nervous system (CNS). VNS is designed to stimulate only the peripheral vagus nerve which contains 80% afferent fibers that terminate in the nucleus of the tractus solitarius in the medulla (Hassan and Al-Quliti, 2014). The tractus solitarius is known to converge in the pons and project to the hippocampus, amygdala, and hypothalamus, all of which are thought to play key roles in seizure onset and propagation (Ricardo and Koh, 1978; Rutecki, 1990). Specifically, some of the afferent fibers converge on the locus coeruleus, and lesions in the locus coeruleus suppress the seizure-attenuating effects of VNS when in animals (Krahl et al., 1998). Even with this knowledge, the exact mechanism by which VNS reduces seizure frequency remains unclear. It seems reasonable to assume that these various brainstem nuclei are involved, and it might even be that VNS is merely a peripheral variation of thalamic stimulation and in this mechanism of action it may resemble deep brain stimulation described below (Ben-Menachem, 2012). Another proposed hypothesis is that VNS may alter synaptic connections by producing a network-modifying influence on the brain (Ben-Menachem, 2012). The last possibility is supported by ample neuroimaging data from PET, SPECT, and fMRI studies indicating sometimes divergent immediate and long-term changes in thalami, cerebellum, orbito-frontal cortex, limbic system, hypothalamus and medulla (Chae et al., 2003).

Development and Uses
The mechanism of action of VNS has been the subject of animal studies since the 1950s and of human studies since 1988 and the device is widely used in clinical settings across the globe (Zanchetti et al., 1952; Chase et al., 1967; McLachlan, 1993). Despite that, its mechanism of action is still not entirely clear. Following two pilot studies demonstrating significant reduction in seizure frequency after VNS treatment in patients with epilepsy refractory to standard AEDs (Uthman et al., 1990; Uthman et al., 1993), a multicenter, prospectively randomized, double-blinded, parallel group study of patients with refractory partial seizures was conducted to evaluate the efficacy and safety of chronic, intermittent VNS (Ben-Menachem et al., 1994). All patients were followed for a 12-week baseline period before being randomized to receive either "high" or "low" VNS stimulation, which acted as a pseudo-control condition. Sixty-seven patients were analyzed after receiving either "high" or "low" stimulation for 14 weeks; the patients who received "high" VNS treatment had a significantly greater reduction in mean seizure frequency (39%) than the patients who received "low" VNS (11%), p = 0.029. A follow-up study published the results from an open-label treatment period lasting 18 months that was conducted with all 67 patients receiving VNS at the "high" stimulation parameters (George et al., 1994). For all patients, mean seizure frequency was reduced by 52% from the 12-week baseline frequency. The results from this multicenter study were promising, so a second multicenter clinical trial, evaluating 254 patients, ages 13–60, with intractable partial seizures was conducted with the same basic design (Handforth et al., 1998). Results showed that patients in the "high" VNS stimulation group had a mean seizure reduction of 28% from baseline while patients in the "low" VNS group showed a 15% reduction. These results, in conjunction with the results from the first multicenter trial, provided the FDA with sufficient evidence to approve VNS as an effective and safe adjunctive treatment for patients with refractory partial-onset seizures, older than 12 years of age.

The previously mentioned report from the Guideline Development Subcommittee of the AAN evaluated the evidence for VNS as a treatment for seizures in children, for the treatment of seizures associated with

Lennox-Gastaut syndrome (LGS), and for improving mood in adults with epilepsy (Morris et al., 2013). A pooled analysis of 481 children with seizures from 14 different Class III studies provided evidence that VNS can effectively achieve > 50% seizure frequency reduction in the children that are responsive to the treatment. A 50% seizure frequency reduction rate was also found in the pooled analysis of 113 LGS patients taken from 4 Class III studies. Data from 2 Class III studies investigating the efficacy of VNS to improve mood found that not only does VNS improve mood, but these improvements are sustained at 6-month follow-up (Elger et al., 2000) and are not correlated with reduced seizure frequency, stimulation frequency, or intensity (Harden et al., 2000). A recent study with a larger sample size also found that VNS is effective at improving mood, as well as quality of life, while not producing negative effects on cognition (Klinkenberg et al., 2012). Following the evaluation of data in the AAN report, the Guideline Development Subcommittee concluded that there is sufficient data for the use of VNS to effectively treat seizures in children and patients with LGS, and the improvement of mood should be considered an additional benefit (Level C) of the treatment (Morris et al., 2013). Furthermore, the report suggested that future research should focus on evaluating the efficacy and safety of the use of VNS in patients with genetic generalized epilepsies. While there is recent evidence from observational studies to suggest VNS may be equally effective at reducing seizure frequency in patients with genetic generalized epilepsies (Thompson et al., 2012), prospective, randomized trials need to be conducted with this population to potentially expand VNS treatment to these patients.

Recently, a non-invasive form of VNS called transcutaneous vagus nerve stimulation (t-VNS) was developed and tested in various clinical populations with promising results. In a proof of concept trial, t-VNS was applied 3 times daily to 10 patients with medication resistant epilepsies over the course of 9 months (Stefan et al., 2012). Although 3 patients dropped out of the study, 5 out of the remaining 7 participants showed an overall significant reduction in seizure frequency, while most scores on cognitive function, mood, and quality of life measures remained stable (Stefan et al., 2012). A larger, controlled trial also demonstrated the efficacy and safety of t-VNS in patients with medication resistant epilepsies (Aihua et al., 2014). Sixty patients were randomly assigned to receive t-VNS in either the Ramsay-Hunt zone (treatment group) or the earlobe (control group) for 12 months (Aihua et al., 2014). After one year of treatment, when compared to the control group, patients in the treatment group exhibited a significantly lower monthly seizure frequency (8 vs. 4; p = 0.003), and had improved mood and quality of life scores (Aihua et al., 2014).

Overall, the long-term safety and tolerability of VNS has been found to be good in over 65,000 patients worldwide, with few reported adverse effects (Hassan and Al-Quliti, 2014). The most common side-effect of VNS is intermittent hoarseness, which occurs in about 28% of patients. Other side-effects include tingling and pain (12%), voice alteration (13%), and cough (Hassan and Al-Quliti, 2014). Very rarely alterations in heart rhythms or pulmonary function can also occur. Adverse effects of t-VNS are low and include headache, hoarseness, and dizziness (Aihua et al., 2014; Stefan et al., 2012). Unlike some of the AEDs, however, VNS has no negative effects on cognition, and has been shown to improve mood. Unfortunately, majority of patients who are responsive to VNS will never achieve complete seizure freedom.

Responsive Neurostimulation (RNS)
RNS is a closed-loop feedback control system that targets the abnormal brain patterns that occur intermittently in patients with epilepsy, while producing no noticeable or significant effects on other brain functions (Liu et al., 2013). In order to detect the dynamic changes at the onset of focal seizure, subdural and depth electrodes are implanted at the epileptogenic area previously identified with direct cortical EEG recordings (Liu et al., 2013). When abnormal activity is detected, the focal point is immediately stimulated, aborting seizure development and propagation before the seizure ever becomes clinically apparent (Liu et al., 2013). The first RNS system was developed by NeuroPace®, Inc. (Mountain View, CA, USA) and this particular device was recently granted approval from the FDA following a randomized, double-blind, sham stimulation controlled study (Ben-Menachem and Krauss, 2014). The NeuroPace® system utilizes a battery-powered device that is surgically implanted into the skull and connected to the subdural and depth leads. This device continuously monitors the patient brain's electrical activity through electrocortigrams (ECoGs) (Fountas et al., 2005). The NeuroPace® system also comes with an interrogation device that allows the physician to program the parame-

ters for the detected ECoG seizures and bursts of electrical activity and to adjust those parameters as needed.

Mechanism of Action

The effects of RNS on seizure control were first published by a succession of human studies conducted by Durland and colleagues in the 1990s. These experiments showed that repetitively delivering neurostimulation directly to an epileptogenic region suppresses *in vitro* spontaneous interictal bursts (Nakagawa and Durand, 1991; Kayyali and Durand, 1991; Warren and Durand, 1998). The pulses generated by RNS create transmembrane currents that cause an inhibitory polarization of the cell membrane that eventually leads to the suppression of seizure activity. It remains unclear, however, whether the stimulation affects the cell membrane channels by altering feedback pathways or by activating inhibitory fibers and neurotransmitters (Montgomery and Baker, 2000; Franaszczuk et al., 2003, Sun et al., 2008). Following Durland's initial studies, brief 50 Hz stimulations were shown to terminate after-discharges (Lesser et al., 1999), providing additional evidence for the anti-epileptic effects of RNS. RNS was shown to reduce epileptiform activity by suppressing the long-range synchrony of gamma-frequency (35–100 Hz) rhythmic activity in intracranial ECoG data (Sohal and Sun, 2011). Most recently, RNS was found to affect EEG spike generation, organization, and topography, suggesting that RNS may affect the underlying interictal epileptic process, not just the ictal patterns that occur during a seizure (Labar et al., 2013).

Development and Uses

NeuroPace®, Inc. is responsible for conducting the first trials demonstrating the safety, efficacy, and feasibility of using a fully implanted closed-loop RNS system (Morrell and Group, 2011). The first multi-center clinical investigation enrolled 65 patients with medically intractable epilepsy to show that the RNS device was safe and well-tolerated by the patients (Barkley et al., 2006). The pivotal study that investigated the use of the RNS system in 191 patients with intractable partial epilepsy in a randomized, double-blind, "sham" controlled study lead to FDA approval of the device in 2014 (Morrell and Group, 2011). In that study, the patients were randomly assigned to either treatment or sham group for a 12-week blinded period, after which all subjects received RNS for an 84-week open-label period. After the 12-week blinded period, seizure frequency was sig-

nificantly reduced in the treatment group that received RNS (–37.9%) compared to the sham group (–17.3%). There was no significant difference in the occurrence of adverse events between the two groups. Later study presented the results collected during the open-label period study reporting that there was a 44% seizure reduction amongst all subjects after 1 year of receiving RNS, and a 52% reduction after 2 years (Heck et al., 2014). This shows that, over time, there was a progressive and significant improvement of seizure reduction with RNS treatment ($p < 0.0001$). The patients typically had several hundred to several thousand irregular spike bursts that triggered RNS each day, resulting in a daily average of 5.9 min of stimulation. Adjustments in stimulation parameters can be made "on-demand" with significant seizure reductions frequently achieved with less than 10 minutes of stimulation per day (personal communication, Dr. Kapur, NeuroPace). After both the blinded and open-label periods, no adverse effects on mood or neuropsychological functioning were observed. Most side-effects of RNS involve infections and discomfort around the implant site. However, up to 20% of the subjects implanted with RNS reported headaches (Morrell and Group, 2011). There is also evidence suggesting that memory impairment and depression can be side effects of RNS in 4% of subjects (Morrell and Group, 2011).

RNS was primarily developed as a treatment option for patients with medically intractable epilepsy that are not candidates for resective surgery. RNS is a viable option over surgery when the location of the epileptogenic site(s) is in a non-resectable zone, such as the eloquent language or motor areas, or when there are two seizure foci (Ben-Menachem and Krauss, 2014). RNS is not appropriate for the treatment of patients with genetic generalized epilepsies who are refractory to standard therapies with AEDs, for treatment of patients in which the epileptogenic site cannot be localized, or for patients with more than two seizure foci. Although RNS was originally developed as a treatment device, it may also be useful (albeit expensive) as an intracranial long-term monitoring system as a prelude for resective procedure in e.g., patients with bi-temporal seizure onset recorded via scalp monitoring (So et al., 2014). In addition, RNS may be a useful tool for improving patient eligibility for surgery. RNS is able to differentiate between unifocal and bifocal epileptogenicity, allowing it the potential to select specific areas for definitive surgical resection (So et al., 2014). In the future, it will

need to be determined whether there are specific sub-populations of patients with epilepsy who benefit more than others (e.g., temporal vs. extra-temporal epilepsies), what are the long-term effects of RNS on mood, what are the cognitive effects (e.g., language, memory) of stimulating eloquent cortex, what are the changes in human cortical physiology that underlie response (or lack thereof) to RNS, and whether the benefits of RNS are also observed in patients who have failed to benefit from previous epilepsy surgery.

Trigeminal Nerve Stimulation (TNS)

TNS is the newest neuromodulation technique to be developed; it involves non-invasive, external (or minimally invasive subcutaneous) stimulation of the trigeminal nerve (DeGiorgio and Krahl, 2013). Conceptually, TNS is similar to VNS, but its ability to stimulate the trigeminal nerve externally and bilaterally provides advantages for this technique over VNS. TNS is also more cost-effective than other neurostimulation devices since it does not require invasive surgery or an extensive hardware system. External TNS (eTNS) is approved for the treatment of epilepsy and depression in adults and children 9 and older in the European Union countries. However, at this time, it remains an investigational device in the United States (MonarchTM eTNS system by NeuroSigma). DeGiorgio and colleagues have completed several trials demonstrating the efficacy of TNS in reducing seizure frequency, which have provided justification for the TNS manufacturer to seek an investigational device exemption from the FDA to conduct a phase III multicenter trial (DeGiorgio et al., 2006; DeGiorgio et al., 2009; Pop et al., 2011; DeGiorgio et al., 2013).

Mechanism of Action

The trigeminal nerve is the largest of the cranial nerves and, like the vagus nerve, it has extensive connections to the brain stem and other structures in the brain (Agur and Dalley, 2009). There are three primary sensory branches of the trigeminal that supply sensation over the face and project to the main trigeminal ganglion at the base of the skull (Agur and Dalley, 2009). Fibers from the trigeminal ganglion are projected to the trigeminal nucleus, which then projects to the nucleus tractus solitaris, locus coeruleus, and the reticular formation, all of which play a role in the inhibition of seizures (DeGiorgio et al., 2011). Thus, the putative mechanism of action may rely on the ability of the TNS system to modulate the function of these targets. However, the exact mechanism by which TNS acts on these brain areas to reduce seizure activity is still unknown. The first study to demonstrate that stimulation of the trigeminal nerve reduces seizure activity was conducted in a rat pentylenetetrazole seizure model (Fanselow et al., 2000). These authors discovered that bilateral TNS stimulation is more effective than unilateral and providing TNS in a closed-loop, seizure-trigger paradigm produces safer and more effective seizure reduction than using a fixed duty cycle. In a recent review article, Fanselow (2012) discussed several additional mechanisms by which TNS may reduce seizure activity. One hypothesis is that TNS causes neuromodulatory activity which then produces desynchronization in the neocortex and hippocampus preventing the activity of neurons that may have gone on to develop into seizures. It may also be that TNS changes thalamic activity through some mechanism, which then prevents the spread of seizures. On a longer time scale, TNS may induce plastic changes that make the epileptogenic tissue less prone to seizures. It needs to be kept in mind that none of these mechanisms of action are mutually exclusive and they each may operate concurrently to reduce seizure activity (DeGiorgio et al., 2011).

Development and Uses

Once animal studies showed that TNS was an effective method for reducing seizure activity, DeGiorgio et al. (2006) conducted a proof-of-concept trial for the use of TNS in human subjects. Supraorbital and/or infraorbital TNS was applied to 7 adult subjects with intractable epilepsy for 3 (N = 5) or 6 (N = 2) months, and resulted in an average seizure reduction of 43.7% from baseline. A follow-up study then published results regarding the long-term feasibility and efficacy of TNS in 12 patients, including the short-term data on the 7 subjects from the original study (DeGiorgio et al., 2009). Compared to baseline, TNS reduced seizure frequency by 66% after 3 months, 56% after 6 months, and 59% after 12 months. Based on these results, these authors decided to conduct an 18-week randomized, controlled study of high vs low (i.e. treatment vs. active control) frequency eTNS in 50 patients with intractable epilepsy (DeGiorgio et al., 2013). After 18-weeks, 40.5% of the patients in the treatment group had >50% reduction in seizure frequency, compared to 15.6% in the active control group. Depression scores on the Beck Depression Inventory also improved from baseline signif-

icantly more in the treatment group compared to the control group, with mean score change −8.13 and −3.95, respectively. This study provided class II evidence that TNS may be a safe and effective treatment for reducing seizures in patients with intractable partial epilepsy.

Overall, TNS has not been shown to be as effective as VNS in reducing seizure activity, but its ability to stimulate non-invasively (eTNS) gives it the advantage of being able to test the efficacy and tolerability of stimulating the trigeminal nerve in each individual before implanting potentially ineffective hardware into a person's body (Fisher, 2011). Based on the randomized, controlled study eTNS is considered a well-tolerated technique, with mild adverse events. Skin irritation was the most commonly reported side-effect (14%), followed by headaches (4%) and anxiety (4%) (DeGiorgio et al., 2013). No significant effects on heart rate or systolic blood pressure were reported in the study. While the research with TNS has only been conducted with adult patients with partial onset intractable epilepsies, its similarity with VNS suggests that it may also be applicable to children and generalized epilepsies but these studies have not been conducted to date.

Deep Brain Stimulation (DBS)

In epilepsy, DBS has been applied to several brain regions as an open loop system to reduce seizure activity. The targets for stimulation were cerebellum, substantia nigra, basal ganglia, and various thalamic nuclei (Morrell, 2006). DBS of the anterior nucleus of the thalamus (ANT) has had the most success at significantly reducing seizures (Fisher et al., 2010) and is now an approved adjunctive therapy in Europe for adult patients with refractory, focal onset epilepsy (Hassan and Al-Quliti, 2014). In DBS, multi-contact depth electrodes are implanted into the ANT using a stereotactic approach (DeGiorgio and Krahl, 2013). Once the target location is identified, cannulas are used to guide the lead electrodes to the target, and then removed once the leads are in place. Unlike DBS for movement disorders, ANT DBS can be performed under general anesthesia because the electrical activity in the ANT is indiscernible from the activity in the surrounding brain regions (DeGiorgio and Krahl, 2013). The stimulator and battery are typically implanted in the chest wall, where it is easily accessible to adjust the parameters in the future (Hassan and Al-Quliti, 2014). Postoperative imaging is crucial to ensuring that the electrodes have proper placement and contact (DeGiorgio

and Krahl, 2013). Recently, a closed-loop neuromodulation prototype of DBS has been developed in an ovine model with the goal to use in epilepsy and other neurological disorder (Afshar et al., 2013).

Mechanism of Action

Similar to other techniques, the mechanism of action behind DBS is poorly understood, with most research involving experimental designs on *in vitro* tissue, animal models, or clinical trials (Graber and Fisher, 2012). In general, DBS is thought to induce disruption of unopposed network activity, specifically high frequency DBS is hypothesized to block epileptiform activity in the cortex, while low-frequency DBS may synchronize cortical activity (Halpern et al., 2009). The ANT is one of the most promising targets for DBS for it is located within the Circuit of Papez which is primarily comprised of the amygdala, hippocampus, fornix, mammillary bodies, ANT and cingulate cortex, and is not only involved in the generation and propagation of epileptic activity (Shah et al., 2012) but also in mood regulation (Allendorfer and Szaflarski, 2014). Given the ANTs position in the Circuit of Papez, stimulation to the ANT is thought to influence the superior-mesial frontal cortex and the mesial temporal cortex, both of which are involved in the patho-anatomy of refractory epilepsy (Graber and Fisher, 2012). Lesions, local injections of muscimol ($GABA_A$ receptor agonist), and high frequency electrical stimulation to the ANT all reduce seizure frequency in several chemoconvulsant models of epilepsy, but *how* this phenomenon occurs is largely unknown (Graber and Fisher, 2012). Most research in this area has focused on the roles of histamine and serotonin, but other neurotransmitters and neuromodulators like glutamate, GABA, and adenosine may also play an important role in this mechanism (Graber and Fisher, 2012).

Development and Uses

The use of DBS to reduce epileptic activity was pioneered by the neurosurgeon, Irving Cooper, who applied DBS first to the cerebellum and then to the ANT (Cooper et al., 1973; Cooper et al., 1980). Although Cooper demonstrated seizure reduction after stimulating both targets, his studies were qualitative, un-controlled, and failed to record important details, such as, comorbidity (Fisher, 2012). DBS to the cerebellum was heavily studied after Cooper's findings with largely inconsistent results, which led researchers to investigate alter-

nate targets, particularly in the thalamus. Stimulation to the centro-median nucleus (CM) of the thalamus was found to terminate spike and slow wave bursts in cats (Psatta, 1983), however subsequent animal studies and small open-label human trials have shown limited efficacy for CM stimulation overall (Morrell, 2006). Bilateral DBS of the ANT has shown the most success at reducing seizures in both animal studies and human trials. Following significant findings in several unblinded and uncontrolled pilot trials (Hodaie et al., 2002; Kerrigan et al., 2004), a multicenter randomized controlled trial of stimulation to the anterior nucleus of thalamus for epilepsy (SANTE) was conducted in 110 adult participants with medically refractory partial seizures, including secondarily generalized seizures (Fisher et al., 2010). Participants were randomized to the stimulation or control group for a 3-month blinded phase, after which all participants received unblinded stimulation. At the end of the blinded phase, there was a 40.4% seizure reduction from baseline in the stimulated group, compared to a 14.5% reduction in the control group. After 2 years of DBS, 54% of participants had a seizure reduction of at least 50% and 14 patients were seizure-free for at least 6 months.

Participants in the stimulation group self-reported significantly more depressive symptoms and memory impairments than participants in the control group, however, neuropsychological test scores for cognition and mood did not differ between the two groups. 12.7% of all participants experienced an infection around one of the surgical sites, leading nine participants to undergo hardware removal. Other adverse events include paresthesia, anxiety, and headache. Overall, the complications found in the SANTE trial are similar to those observed with DBS use in movement disorders (Fisher, 2012). Interestingly, the SANTE trial also discovered that participants with temporal lobe seizures responded better to DBS than participants with seizure onsets in other lobes or those with multifocal seizures (Fisher et al., 2010). Fisher et al. (2010) hypothesized that this phenomenon may reflect the participation of the mesial temporal lobe and the ANT in the circuit of Papez. Based on the current amount of data, it is generally recommended at this time that patients consider surgical resection or VNS before undergoing DBS (Hassan and Al-Quliti, 2014).

Transcranial Direct-Current Stimulation (tDCS)
Transcranial direct-current stimulation is a form on non-invasive brain stimulation that was originally described in the 1960s, but didn't gain clinical popularity until the early 2000s. In tDCS, of the two surface electrodes placed on the scalp one serves as the anode and the other one as the cathode, while a direct current, ranging from <1 mA to 2 mA, flows between the electrodes (Been et al., 2007). On average, half of the injected tDCS current is shunted through the scalp, but this is dependent on the dimension and position of the electrodes (Miranda et al., 2006). Specifically, increasing the distance between the cathode and the anode results in decreased shunting through the scalp, and therefore, increased current flows into the brain (Miranda et al., 2006). Depending on the direction and intensity of the current that passes through the brain, tDCS will increase or decrease cortical excitability (Been et al., 2007). Typically, anodal tDCS depolarizes local neurons, thereby increasing cortical excitability, while cathodal tDCS hyperpolarizes neurons to produce an inhibitory effect (Nitsche et al., 2007). Since epileptogenic activity is characterized by increased cortical excitability, cathodal tDCS may be used to reduce seizure frequency in epilepsy patients. After one session of 1 mA tDCS applied continuously for 9–20 minutes, cortical excitability changes remain stable for up to one hour post-stimulation, while the use of pharmacological agents can prolong these after effects for several more hours (Nitsche and Paulus, 2000). A repetitive protocol in which one session of tDCS is applied daily over the course of several days or weeks may prolong these effects even longer. The optimal protocol for tDCS has yet to be established, with important questions regarding optimal stimulation duration, repetition rate, reference electrode position, and stimulation strength still unanswered (Nitsche and Paulus, 2009).

Mechanism of Action
Cathodal tDCS creates short-lasting and long-lasting effects, both of which possess different underlying mechanisms (Nitsche et al., 2005). The short-lasting effects are primarily dependent on the activity and homeostasis of sodium and calcium ions, which are responsible for maintaining the stability of the membrane potential (Liebetanz et al., 2006). In contrast, the long-lasting after-effects of tDCS are likely mediated at the synaptic level by N-methyl-D-aspartate (NMDA) receptors (Liebetanz et al., 2002). To specifically investigate the underlying mechanisms of the long-effects of cathodal tDCS on cortical excitability, Ardolino et al. (2005)

stimulated the central and peripheral nervous systems and measured the effects on spontaneous neural activity and evoked motor responses. Based on changes in neural membrane function, they found that the long-lasting, after-effects of tDCS are non-synaptic in nature. Rather, it's hypothesized that tDCS may alter the neural membrane by changing local ionic concentrations, altering transmembrane proteins, or causing electrolysis-related changes in [H+] through its constant electric field to create its long-lasting effects (Ardolino et al., 2005).

Development and Uses

To demonstrate the anticonvulsant potential of tDCS, Liebetanz et al. (2006) applied weak tDCS to the sensorimotor cortex of rats in a modified cortical ramp-stimulation model of focal epilepsy. The stimulation significantly increased seizure threshold in the rats for up to 90 minutes post-stimulation. Based on the promising results from several animal studies, a randomized, controlled clinical trial was conducted to investigate the safety and efficacy of using cathodal tDCS to reduce epileptic activity in patients with refractory epilepsy and malformations of cortical development (MCSs) (Fregni et al., 2006). Nineteen patients were randomly assigned to receive one session (20 min) of active (1mA) or sham cathodal tDCS, and the number of epileptic discharges (EDs) and seizures were measured at baseline, immediately after, 15 days after, and 30 days after stimulation. Compared to baseline, patients receiving active cathodal tDCS had significantly greater reduction in EDs immediately after stimulation (−265.9) than those who received sham (−19.4), p = 0.049. Seizure frequency showed a decreasing trend in the active treatment group, however results were not significant. Results from this study demonstrated the efficacy of cathodal tDCS as a non-invasive neurostimulation technique for the treatment of epilepsy. Following these results, a similar study using the same tDCS parameters was conducted to establish the safety and anti-epileptic effects of cathodal tDCS in children with refractory childhood focal epilepsy (Auvichayapat et al., 2013). Significant reductions in EDs were found in the active group immediately, 24, and 48 hours after stimulation, and no adverse events occurred in either group.

A safety study conducted on 102 healthy subjects and patients of various clinical populations found that the most common adverse effect of tDCS is a mild tingling sensation (70.6%), followed by fatigue (35.3%),

itching under the electrodes (30.4%), and headaches (11.8%) (Poreisz et al., 2007). While in humans tDCS has primarily been applied in focal epilepsy, a recent study demonstrated successful abatement of generalized seizures by using a closed-loop tDCS in a rodent model of genetic generalized epilepsy (Berényi et al., 2012). Overall, the role of tDCS in the treatment of epilepsy is not yet established. Future studies should utilize larger samples sizes and establish the efficacy of tDCS for various epilepsy populations. Furthermore, a protocol that employs more than one application of tDCS should be considered, and may improve the long-term effects of tDCS.

Repetitive Transcranial Magnetic Stimulation (rTMS)

Single-pulse transcranial magnetic stimulation was originally proposed as a noninvasive brain stimulation technique in the mid-1980s, and was used as a diagnostic tool for measuring cortical excitability in epilepsy patients (Kimiskidis et al., 2014). In single-pulse TMS, a stimulator produces a strong magnetic current and sends it through a coil placed on the scalp in pulses at intervals that can be set individually and at least several seconds apart. The coil delivers the magnetic current through the skull which induces an electric current in the brain that elicits action potentials in cortical neurons approximately 1.5–2.0 cm beneath the scalp (Epstein et al., 1990). Animal studies showed that if the electrical current *repetitively* activated these cortical neurons, long-lasting changes in cortical excitability will have occurred, leading to the discovery of rTMS (Nitsche and Paulus, 2009). The type of excitability change is determined by the frequency of the repeated pulses, such that low-frequency rTMS (≤ 1 Hz) reduces cortical excitability and high-frequency rTMS (> 1 Hz) increases cortical excitability (Pascual-Leone et al., 1998) but these changes are not necessarily synonymous with increased inhibition or excitability, respectively. Both focal and generalized epilepsies are characterized by increased cortical excitability. Thus, in 1993, Reutens et al. used TMS to show that AEDs reduce cortical excitability in patients with epilepsy, suggesting that low-frequency rTMS may potentially be a useful therapeutic tool for evaluating the effects of treatments on cortical excitability and for reducing cortical excitability in patients resistant to AEDs.

An EMG is typically used in conjunction with rTMS to determine the ideal stimulation intensity for each in-

dividual. rTMS is typically applied to the primary motor cortex (M1), one of the most epileptogenic brain areas (Penfield and Jasper, 1954), and the motor evoked potentials (MEPs) that result from the stimulations are recorded with surface EMG electrodes placed at the targeted muscle. The individual's motor threshold (MT) is then determined, and is defined as the minimum intensity required to produce at least 5–10 consecutive MEPs usually between 50–100 mV (Rossini et al., 1994). The intensity is represented as a function of the maximum output of the stimulator being used, meaning the individual MT will often vary depending on the machine that is used. The type of coil also affects MT, so to reliability compare MTs, the same stimulator and coil should be used. Intensity is represented as a function of individual MT to ensure that the stimulations are safe, yet effective, for everyone, and it allows for stimulation intensity to be comparable across individuals.

Mechanism of Action

Although the magnetic field produced by rTMS typically penetrates only 1.5–2.0 cm beneath the skull to activate local neurons, based on the spatial orientation and diameter of the neuronal axons, the effects of rTMS can occur at a distance from the stimulation site (Lefaucheur et al., 2014). Thus, the orientation and position of the coil over the designated gyrus or sulcus is critical for determining the direction that the electrical current will flow in the brain, and consequently, which brain regions will be affected (Lefaucheur et al., 2014). For optimal stimulation, the coil should be placed flat on the scalp and oriented tangential (45° angle) to the midline, so that the current flows in a postero-anterior direction (Di Lazzaro et al., 2008). A figure-of-eight coil is primarily used in rTMS studies attempting to stimulate the epileptogenic site because it produces the strongest current in the center, where the two round components intersect, allowing for greater focal stimulation than a circular coil (Tassinari et al., 2003). The "inhibitory" aspect of low-frequency rTMS and the "excitatory" aspect of high-frequency rTMS are often compared to the effects of long-term depression (LTD) and long-term potentiation (LTP) that are found in animal models. However, the effects of high- and low-frequency rTMS are actually mixed under various conditions (Houdayer et al., 2008e), so LTP and LTD are not likely to be the underlying mechanisms of action. Furthermore, high-frequency rTMS can produce "excitatory" effects by inhibiting the inhibition network

and low-frequency rTMS can produce "inhibitory" effects through excitation of the inhibition network making the underlying mechanisms of rTMS highly variable (Lefaucheur et al., 2014).

Development and Uses

Based on promising findings from animal studies (Weiss et al., 1995; Jennum and Klitgaard, 1996), Tergau et al. (1999) conducted a pivotal, open pilot study investigating the effects of low-frequency rTMS on 9 adult patients with refractory focal epilepsies. The rTMS protocol was done for 5 consecutive days and consisted of two trains of 500 pulses applied at a frequency of 0.33 Hz through a circular coil placed over the vertex. Mean seizure frequency in the four weeks post-stimulation was significantly reduced compared to the mean seizure frequency in the four weeks prior to stimulation (p = 0.048). Following this study, a succession of single case reports and open label trials using a variety of methods on different epilepsy types were published with mixed results. The first randomized, blinded, control trial randomly assigned 24 patients with a localization-related epilepsy to either low-frequency (1 Hz) rTMS at 120% MT or a sham rTMS condition (Theodore et al., 2002). rTMS was delivered through a figure-of-eight shaped coil to the putative epileptogenic focus for 15 minutes twice a day for 1 week. While the actively treated patients showed a greater reduction in seizure frequency than the sham-stimulated group, the results of this possibly underpowered study were not significant, and the effect of rTMS on seizure frequency was found to be minimal and short-lived. The following randomized, double-blinded and controlled study applied focal, low-frequency rTMS at a fixed intensity (70% max output) to patients with malformations of cortical development and refractory epilepsy for five consecutive days (Fregni et al., 2006). Results showed a significant seizure reduction in the active group compared (n = 12) to the sham group (n = 9) (p < 0.0001) that lasted up to two months after stimulation. There was also a significant reduction in EDs in the active group that lasted for one month following stimulation. A recent controlled clinical study randomly assigned 60 patients with refractory focal epilepsy to receive low-frequency rTMS at 90% MT or 20% MT (control) applied to the putative epileptogenic focus (Sun et al., 2012). In 90% MT group, frequency of seizures and EDs was significantly reduced from baseline following 2 weeks of rTMS. rTMS was also found to significantly improve the psy-

chological conditions of patients in the 90% MT group.

Overall, the data are mixed, primarily due to variations in stimulus intensity, stimulation site, number of stimuli, treatment duration, and seizure/epilepsy diagnosis. The placebo effect produced by the various sham rTMS conditions may also be problematic (Bae et al., 2011), and the employment of a standard sham condition method may be useful when comparing results across studies. All randomized, controlled studies have used patients with focal epilepsies, so the efficacy of rTMS for patients with genetic generalized epilepsies and the location for stimulation in these patients have yet to be established. Because rTMS primarily affects cortical areas up to 1.5–2 cm beneath the skull, patients with epileptogenic foci in subcortical (deep) regions are unlikely to significantly benefit from rTMS. A literature review investigating the adverse effects of rTMS in patients with epilepsy found that adverse events occurred in 17.1% of patients, with the most common being transient headaches (9.6%) and general feelings of discomfort and weakness (Bae et al., 2007). While there have been some reported cases of seizures induced by rTMS, this was found to be a rare event with a crude risk of 1.4%.

CONCLUSIONS

Great progress in neurostimulation and neuromodulation has been made over the last two decades with 2 devices (VNS, RNS) approved for the treatment of epilepsy in the US and three (DBS in addition to VNS and RNS) in Europe based on the results of the randomized controlled trials (Ben-Menachem et al., 1994; Handforth et al., 1998; Morrell and Group, 2011; Heck et al., 2014). Other devices and modalities do not have sufficient evidence to support or refute their use in a clinical setting. As the number of devices and modalities increases, the clinician is left with choices that are not simple – at which time should neuromodulation/neurostimulation be introduced as a possible treatment option, which device is best for which patient, what should be done first – device implantation vs. detailed presurgical evaluation, should patients with genetic generalized epilepsies be implanted with VNS or DBS or treated with rTMS or TNS, or whether neuromodulation/neurostimulation should be used in place of standard AEDs. While answers to these questions supported by scientific data are not available today and are left largely to the experience and preference of the treating epilepsy specialist, clinicians and patients should be aware of these choices so that they both can make an informed decision. The future of neuromodulation/neurostimulation is exciting – while various studies and efforts are underway and will provide us with more data in the future, the one clear advantage of these treatments/devices is the consistently noted continuous improvement in seizure control over time – something that the AEDs have thus far failed to deliver. Future studies will need to determine the short- and long-term efficacy of rTMS, tDCS, t-VNS etc. and provide data that compare the efficacy of these modalities.

CONFLICT OF INTEREST DISCLOSURE

The authors declared no conflict of interests in conjunction with the content of the manuscript to report.

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