Review article

Neocortical electrical stimulation for epilepsy: closed-loop versus open-loop

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Abstract

The aim of this review is to evaluate whether open-loop or closed-loop neocortical electrical stimulation should be the preferred approach to manage seizures in intractable epilepsy.

Twenty cases of open-loop neocortical stimulation with an implanted device have been reported, in 5 case studies. Closed-loop stimulation with an implanted device has been investigated in a larger number of patients in the RNS System clinical trials. With 230 patients enrolled at the start of the Long-term Treatment Trial, 115 remained at the last reported follow-up. Open-loop stimulation reduced seizure frequency in patients on average with over 90% compared to baseline. Closed-loop stimulation reduces seizure frequency with 60%-65%.

Even though open-loop neocortical electrical stimulation has only been reported in 20 patients, and closed-loop in much a larger sample, evidence suggests that both approaches are effective in reducing seizures. It remains an open question which should be clinically preferred. Therefore, a head-to-head adaptive clinical study comparing both approaches is proposed.

Keywords

brain stimulation; cortical electrical stimulation; epilepsy; open-loop; closed-loop

1. Introduction

Intractable epilepsy is a condition in which seizures cannot be controlled by antiepileptic drugs (AEDs). Perhaps the most effective treatments for those patients are resective surgery and laser ablation (Curry et al. 2012; Gonzalez-Martinez et al. 2014) of the epileptogenic tissue. However, for some patients, surgery might fail to control seizures, due to mislocalisation of the epileptogenic focus (Salanova, Markand, and Worth 2005), insufficient resection, as well as other factors (Harroud et al. 2012). When surgery is ineffective or not recommended, electrical stimulation has been used as an alternative treatment for medically intractable epilepsy. The most prevalent method is vagus nerve stimulation (VNS). Another is deep brain stimulation (DBS), and targets that have been chosen include the hippocampus, anterior thalamic nuclei, centromedian nucleus, caudate nucleus and the cerebellum. Non-invasive transcranial magnetic stimulation (TMS) generates intracranial electrical currents that may similarly influence cortex excitability (Lundstrom et al. 2017) and could decrease seizure frequency (Sun et al. 2012). Since TMS is not a wearable device, it is outside this review.

An alternative method to manage seizures is by cortical electrical stimulation (CES) directly to the seizure focus. It has been shown that electric pulses can suppress epileptiform activity (Kinoshita et al. 2004, 2005; Kossoff et al. 2004; Lesser et al. 1999; Schrader et al. 2006; Yamamoto et al. 2002, 2006) or reduce seizure rate after short-term continuous CES (Valentin et al. 2017; Valentín et al. 2016). CES can be performed either in an open-loop, or in a closed-loop approach. The open-loop method uses pre-scheduled stimulation, irrespective of ongoing electrophysiological activity in the brain. It is also referred to as “chronic” stimulation, when it is continuous. VNS and DBS are usually delivered in an open-loop manner. Their targets are not neocortical and are therefore beyond the scope of this review. Neocortical open-loop stimulation for epilepsy is a novel approach, which has not yet been extensively clinically tested.

Closed-loop CES means that stimulation starts in response to signals of an impending seizure. It is hence also termed ‘responsive stimulation’ and aims at preventing or early termination of the clinical symptoms of seizures. To achieve this, electrical brain activity is continuously monitored with subdural implanted electrodes (electrocorticography (ECoG)). Upon detection of abnormal patterns, CES is delivered to terminate seizure onset. Closed-loop neocortical stimulation has been studied in more patients compared to open-loop.

1.1. Available devices

The RNS System (by Neuropace) is currently the only fully implantable responsive neurostimulator. The procedure involves a craniotomy and the implantation of the neurostimulator within the curvature of the skull. The whole device is then covered by the scalp. Two electrode leads are connected to the stimulator to monitor and deliver treatment to up to two seizure onset zones.

In all case studies, Medtronic neurostimulators were used for chronic open-loop stimulation. Unlike the RNS, this stimulator is implanted in the chest, rather than within the curvature of the skull. Although typically used for DBS, ECoG leads can also be attached.

1.2. Scope and significance of the review

This review compares open-loop and closed-loop CES, delivered to the neocortical seizure focus. So far, there has been no scientific or medical consensus on which approach is superior to the other, or which method should be preferred in any individual case. Therefore, this review seeks to establish whether open-loop or closed-loop CES should be the clinically preferred method for reducing the frequency and severity of epileptic seizures. The following specific review questions are addressed:

- Which method, open-loop or closed-loop CES, results in a bigger reduction of seizure frequency and severity in the long-term (more than 1 year after the start of the treatment)?
- Which method results in dramatic seizure frequency/severity reduction faster (i.e. how long after onset of treatment)?
- Which method carries less risk of adverse effects for the patient?
- Which method is more practical from the technical perspective (eg. battery life)?

2. Methods

2.1. Inclusion criteria

Inclusion criteria for article selection were:

1. CES to a neocortical seizure focus was performed with an implanted device with the goal of reducing seizure frequency/severity.
2. Either open-loop or closed-loop CES was delivered.
3. Large sample clinical studies when available, otherwise – case studies.
4. Human studies only.
5. Data published in original articles, research letters and supplementary material.

6. Year of publication: 1990 – 2017.
7. Language of publication: English.

2.2. Search strategy

The article search was performed in PubMed. Keywords were: cerebral; cortex; electrical; stimulation. Articles were chosen based on the inclusion criteria. Additional articles were chosen from the reference lists of already included publications.

2.3. Data collection and analysis

The data for this review were collected from the results sections of the chosen articles and/or supplementary materials. The data of interest included number of participants, study design, type of seizure, seizure focus location, stimulation parameters, type of treatment (open/closed-loop), duration of treatment, seizure frequency before treatment, percent seizure frequency reduction shortly after onset of treatment (immediately up to 1 year), percent seizure frequency reduction in the long-term (1 year and above after onset of treatment), percent of patients with adverse side effects/adverse events, and, if available, improvements in quality of life, including improvements in cognitive and non-cognitive (eg. motor) functioning.

The percentages of seizure reduction between methods were compared. Meta-analyses were not performed due to the different study designs of the chosen articles.

3. Results

3.1. Selected articles

The search in PubMed resulted in 940 articles. After reading titles, abstracts, and total articles, only eight articles were selected for review (for details, see Supplementary materials - Table 1). For the closed-loop paradigm, three publications were chosen, which present the results from the Pivotal RNS System clinical trial and the Long-term Treatment Trial (LTT): (Heck et al. 2014; Morrell 2011) – Pivotal trial; (Bergey et al. 2015) – LTT trial).

For open-loop stimulation five articles, presenting case reports, were selected: (Elisevich et al. 2006) – 1 patient; (Velasco et al. 2009) – 2 patients; (Child et al. 2014) – 2 patients; (Valentin et al. 2015) – 2 patients, (Lundstrom et al. 2016) – 13 patients. To our knowledge, those are the only publications to date which report data from open-loop neocortical electrical stimulation for epilepsy.

3.2. Closed-loop stimulation

3.2.1. Study design

The RNS System Pivotal trial started with a 3-month baseline period, in which seizure frequency was evaluated. Patients had to have at least three disabling seizures per month (while on AEDs) to be eligible for implantation. Surgery was performed at the end of the baseline period. It was followed by a 4-week post-op stabilization period with ECoG monitoring and no stimulation. At the end of the monitoring phase, the patients were randomized into a treatment group and sham group. A 4-week stimulation optimization period followed, in which stimulation parameters were adjusted. The blinded evaluation phase started at 8 weeks' post-implant and continued for 3 months. During this period, only the patients in the treatment group received stimulation. The neurostimulators in the sham group were not programmed to deliver treatment, but patients had undergone sham programming. AEDs were kept constant in the blinded phase. At month 5 after implantation (end of blinded period), all patients transitioned into the open label phase. All patients received stimulation from this moment onwards. AEDs could be adjusted in this period. The end of the open label period continued until 2 years after implantation.

The LTT trial scope was from year 2 (end of open label period of Pivotal trial) onwards. The same patients from the Pivotal trial transitioned into the LTT. Some had dropped out.

Changes in seizure frequency during both the Pivotal and LTT trials were compared against the pre-implant baseline period.

3.2.2. Patient demographics

A total of 256 patients were implanted with the RNS System. 65 patients were implanted in an initial Feasibility study, which is not discussed here. 191 patients were implanted in the Pivotal trial. 187 of them completed the blinded phase, 182 reached one year post-implant and 175 reached two years post-implant. Participants in the LTT included patients who had completed the Pivotal trial, as well as patients who had participated in a previous Feasibility study, with a total of 230 patients. The number of patients that reached year 6 of the LTT was 115. The mean follow-up period was 5.4 implant years.

Around 50% of patients in both trials had seizure foci on neocortex (specific locations not reported), 7% had combined neocortical and mesial temporal lobe epilepsy (MTLE). The rest had mesial temporal lobe epilepsy (MTLE). Seizure types included simple partial motor seizures, complex partial seizures and secondarily generalized tonic-clonic seizures.

Around one third of patients had prior epilepsy surgery, one third had undergone VNS and one third had been hospitalized for ECoG monitoring.

3.2.3. Stimulation parameters

Stimulation was delivered at 200Hz, pulse width at 160 μs, burst duration of 100msec. Current amplitude was below 4mA in 53.8% of subjects, between 4 and 7.9mA in 34.8% and between 8-11.9mA in 8.7% and 12mA in 2.7% of all patients at the end of the open label of the Pivotal trial.

3.2.4. Seizure reduction

In the first month of the blinded period, there was a 34.2% reduction in seizures for the treatment group. Seizure frequency continued to improve in the three-month post-implantation period (mean - 37.9%), which was the end of the blinded phase. In the sham stimulation group, there was an initial effect of 25.2% reduction in seizures, but until the end of the 3-month period seizure frequency increased and was 9.4% less compared to baseline (mean reduction for blinded phase: - 17.3%). Reductions in seizures were similar in those with MTLE and neocortical onsets, in those with one and two seizure onset zones, in patients with and without prior intracranial monitoring, and in those treated with and without prior treatment with VNS or epilepsy surgery.

The median seizure reduction for year 1 was 44%; for year 2, 53%. At the end of the open-label period: 58% seizure reduction was reported for the patients with non-MTLE. MTLE patients had a 55% reduction in seizure frequency. Responder rate (patients with 50% or more reduction in seizures) was 29% for the treatment group and 27% in the sham group during the blinded period. In the last three months of the open-label phase 54% of patients had a reduction in seizure frequency of 50% or more. However, 7% had an increase in seizure frequency of 50% or more, 9% were seizure free over the last three months of the Pivotal trial.

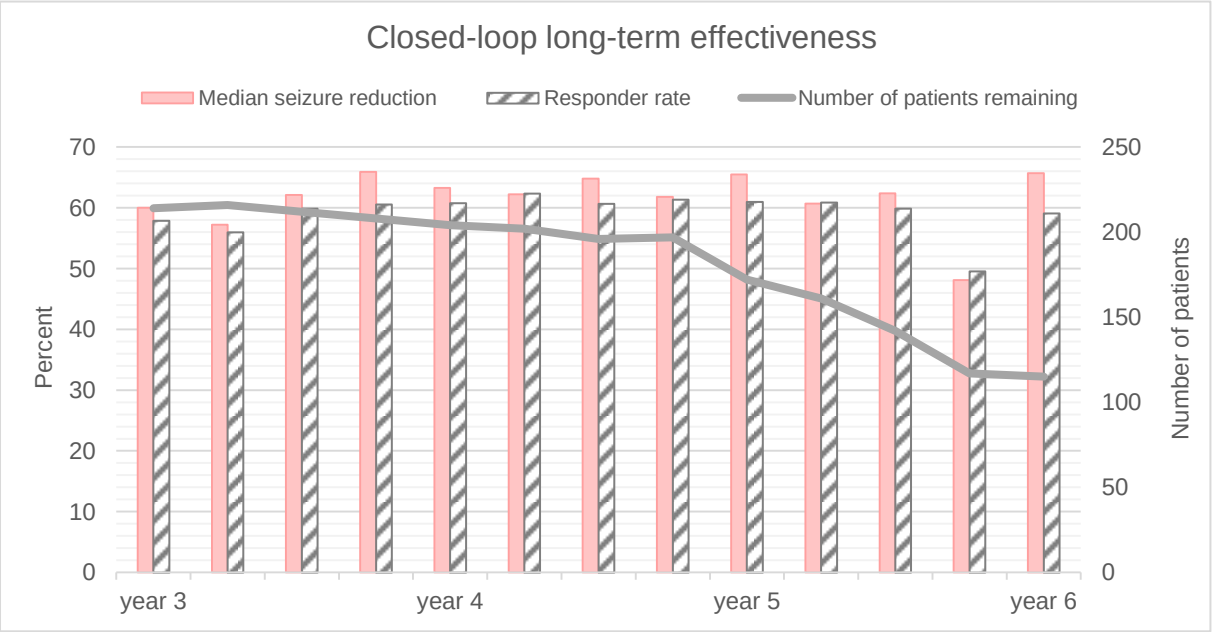

Figure 1. Results from the RNS Long-term treatment trial. Data from Bergey et al., 2015.
Data is not adjusted for dropped-out patients. Each group of bars represents a three-month period from the beginning of year 3 until the beginning of year 6 (13 3-month periods in total). The filled bars show median seizure frequency reduction in percent compared to pre-implantation baseline. The striped bars represent the responder rate in percent. Responders are patients who have seizure frequency reduction of 50% or more. The grey line represents the number of participants enrolled at each time point.

Figure 1 presents the long-term efficiency of closed-loop stimulation. At the first three-month period of year 3 (start of LTT) the median percent reduction of seizures was 60% (n=214 after patient drop-out) and the responder rate for that time point 58%. This responder rate included only the patients currently enrolled in the study. However, the adjusted responder rate, which also included patients who had withdrawn from the trial, was also 58%. At this stage, all implanted patients had the neurostimulator turned on and delivering treatment. The rates of seizure reduction varied between 48% and 66%. For the last three months of the LTT (beginning of year 6), the median percent reduction was 66%. 115 patients reached year 6 in the ongoing study, at the date of publication. The adjusted responder rate at year 6 was 55.6%.

Out of all 256 implanted patients before the start of the trials, 36.7% experienced at least one 3-month or longer seizure-free period, 23% at least 6-month seizure free or longer, and 12.9% were seizure free for at least 1 year. No participant was seizure-free for the entire period of the studies and no improvements in seizure severity were reported.

3.2.5. Adverse effects

The most prevalent adverse effect throughout the trials was infection of the implant site (9.4% of patients). 4.7% of the patients experienced some type of intracranial hemorrhage. The number of implantation-related adverse events was not higher compared to that reported

following implantation of intracranial electrodes, epilepsy surgery, or with DBS devices for treatment of movement disorders.

Additionally, 7.8% experienced an increase in complex partial seizures. The frequency of tonic-clonic seizures increased in 5.9% and severity of tonic-clonic seizures increased in 4.7% of the patients. Number of seizure-related adverse events was not higher than in medicinal trials for partial onset seizures.

The device had to be removed in 5.5% of patients. Battery was prematurely depleted in 4.7%. Other adverse events reported by (Bergey et al. 2015), which occurred in 2.5-4.5% patients are death, device lead damage, depression/suicidal (not related to neurostimulation), device lead revision, non-convulsive status epilepticus, pneumonia, convulsive status epilepticus, skin laceration due to seizure, suicide attempt. Number of deaths were not more frequent than expected in patients with refractory epilepsy.

3.2.6. Quality of life

Quality of life improved after year 1 after onset of treatment and remained stable until year 5. Significant improvement was present in the following QOLIE-89 scales: seizure worry, health discouragement, attention, concentration, work/driving/social function, language, role limitation (physical), memory, energy/fatigue, medication effects, overall quality of life.

3.3. Open-loop stimulation

Five case studies on open-loop neocortical stimulation were selected, presenting 21 cases in total. One of the cases presented by (Child et al. 2014) only underwent trial stimulation (authors do not report duration of trial stimulation) and did not get a permanent implant. Therefore, this case was not included in this review. In the scope of this review are 20 cases (14 male, mean age 21, range 6-56) with seizure foci on primary motor cortex (7), supplementary motor cortex (SMA) (1), with both foci on both eloquent motor and language cortex (1), seizure foci on parietal cortex (3), frontal cortex (2), temporal cortex (2), and one patient with no observed lesion. In three patients reported by (Lundstrom et al. 2016), only pathology was mentioned: scattered encephalomalacia (1), hemisphere infarct (1), or middle cerebral artery infarct (1). Four patients were diagnosed with epilepsia partialis continua (EPC). Patients had predominantly simple partial motor seizures, secondary tonic-clonic seizures, focal dyscognitive seizures and occasionally secondarily generalized seizures or reflex seizures. One patient had postictal face and corporal paresis (Todd's phenomenon);

another had a transient postictal motor disability of the affected arm. Jacksonian march had also been observed in this patient.

3.3.1. Stimulation parameters

Seventeen patients had continuous chronic stimulation. Two patients had cyclic stimulation (1 min on - 4 min off; 3 min on - 10 min off) and one patient first received continuous, and subsequently cyclic (1 min on - 4 min off) to preserve battery life. Pulse rate was between 2 and 130 Hz and pulse width between 90µs and 120ms. Up to 7V and 3mA were used. The minimum current intensity used was below 450 µA (Velasco et al. 2009).

3.3.2. Seizure reduction

Chronic stimulation resulted in a reduction of seizure frequency by more than 90% in 8 out of 16 cases in the first year (Figure 2). One case (female, age 17) with smaller reduction in month 1, became seizure free in month 2, when stimulation intensity was increased from 250µA to 350µA. Another case (male, age 44) was stimulated with 50 Hz and experienced a gradual decrease in seizure frequency, with a mean reduction of around 80% in month 2, around 90% in month 6, and 4 years after implantation, seizures were more than 97% less frequent. The short-term reduction of seizures was not mentioned for one patient (Child et al. 2014). For 3 patients (patient 8, 14, 17 in Figure 2), no seizure reduction was mentioned because these patients had reflex seizures or EPC (Lundstrom et al. 2016).

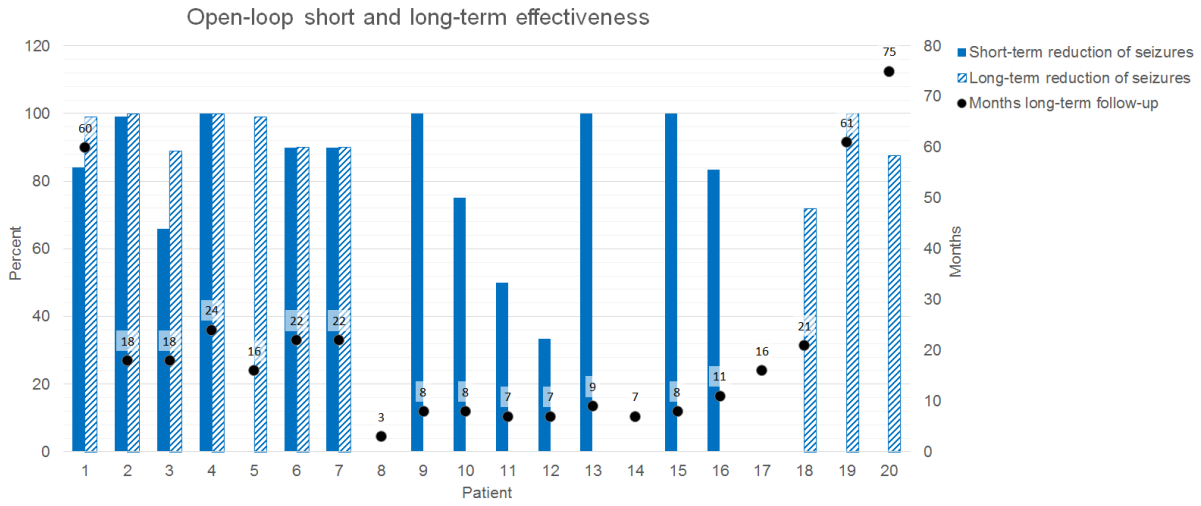

Figure 2. Open-loop short versus long-term effectiveness.
Data from (Elisevich et al. 2006), (Velasco et al. 2009), (Child et al. 2014), (Valentin et al. 2015) and (Lundstrom et al. 2016). The filled bars represent short-term percent reduction of seizure frequency (within one year post-implantation). Short-term data for patient 5 (Child et al. 2014), and seizure reduction due to the presence of EPC or reflex seizures for patient 8, 14 and 17 (Lundstrom et al. 2016) was not reported. Striped bars represent long-term percent reduction at last follow-up post-implantation (indicated by the dark boxes and the right vertical axis).

All patients experienced dramatic (72-100%) reduction in seizure frequency in the long-term (above 1 year of treatment) (Figure 2). Additionally, postictal events like Todd's phenomenon (2 patients) and motor dysfunction (1 patient) were eliminated. There was also a reduction of over 90% of IEDs in two patients. In another, they gradually decreased until month 12, when they had completely disappeared.

(Child et al. 2014) and (Valentin et al. 2015) report that when the stimulator was deactivated (due to battery depletion or inadvertently), seizure frequency increased close to the baseline level, and decreased once treatment was resumed.

3.3.3. Adverse effects

There were no adverse effects in any of the cases, neither related to the implantation of the leads or neurostimulator, nor the stimulation itself. The only adverse events occurred when battery was depleted and seizures/EPC reappeared. However, they were resolved once stimulation was resumed.

3.3.4. Quality of life

(Velasco et al. 2009) measured quality of life before and after treatment using the QOLIE scale for adolescents. For one of the cases (male, age 17), a total of 17.56 improvement was present in the scales impact, memory, stigma, support and health. For the other case (female, age 17), there were improvements in impact, memory, functioning, stigma, support, school and attitudes, with a total of 33 points. It should be noted that the second case had mental retardation. Both patients had aggressive attitudes before the treatment, which were resolved in the first patient.

(Lundstrom et al. 2016) determined life satisfaction based on patient self-report. Ten of the 13 patients reported increased life satisfaction following chronic stimulation (4.5 (SD:2.2) to 7.2 (SD: 1.6)).

The other case studies did not report formally measured quality of life changes, but observed significant improvements in motor function. One of the patients reported by (Valentin et al. 2015) had significantly better hand dexterity and fine motor control, and could perform tasks like drawing and writing, which were not possible before, due to the EPC. The main improvement in the case reported by (Elisevich et al. 2006) was that the patient no longer had the postictal motor disability of the hand, which prevented him from operating his arm for 30 minutes after seizure-related tonic posturing.

4. Discussion

Eight articles were selected for review. Three articles reported the RNS System clinical trials, which evaluated closed-loop stimulation for epilepsy. Around 50% of those patients had neocortical epilepsy with varying seizure onset zones. Five case reports on open-loop neocortical stimulation were selected for review, describing the treatment outcome in 20 patients, 8 of which with seizure foci in motor cortex, and 4 with motor seizures but unspecified seizure foci.

4.1. Quality of evidence

There is a strong publication bias, as the closed-loop articles reported well-controlled large-sample clinical trials, while the open-loop articles were only case reports. The quality of evidence for the clinical trials was moderate, as the study design did not include control for seizure focus location, which can prove to be important for treatment effectiveness. Due to the descriptive nature of the case reports, their quality of evidence is low. At this point in time, this is unavoidable. Open-loop stimulation has only been extensively used with non-neocortical targets, such as the vagus nerve, the hippocampus, the centromedian nucleus, the caudate nucleus and the anterior thalamic nucleus. To our knowledge, the articles selected in this review - (Child et al. 2014; Elisevich et al. 2006; Lundstrom et al. 2016; Valentin et al. 2015; Velasco et al. 2009), are the only published data to date on open-loop electrical stimulation delivered to neocortical seizure focus. Those five articles present 20 cases with long-term (aiming at permanent) implantation of a chronic neurostimulator.

4.2. Effectiveness of closed-loop versus open-loop

No conclusions can be made based on the currently available data. Until more empirical data and knowledge is accumulated, all discussions are speculative.

Both approaches appear to be effective in reducing seizure frequency in patients with medically intractable epilepsy. However, open-loop neocortical stimulation seems to provide a more drastic change in seizure frequency reduction (on average over 90%). In the short-term, open-loop seems to offer a faster result. However, the RNS Pivotal study showed that there is an initial implantation effect, which drove the reduction of seizures in the first few months. Both the treatment and the sham group experienced less seizures in the short-term. However, the reduction continued to lower for the treatment group, while in the sham – it started rising again after 3 months. It is very likely that the same effect was also contributing to the results presented in the open-loop case studies. Even so, the seizure frequency reduction

in those patients was quite drastic, with some patients experiencing more than 90% less seizures immediately after onset of treatment. One patient who had a delayed response was initially treated with a lower stimulus intensity. When it was increased, seizure frequency dropped. This immediate reduction in seizures after onset of stimulation, with the electrode leads having been implanted for a long period, reduces the probability of a placebo effect.

For the purposes of this review, we considered long-term effectiveness of seizure reduction at the last follow-up that was reported. The open-loop case studies present results from follow-ups between 3 months and 6 years. The RNS clinical trials' last reported follow-up was 5 years and three months (i.e. first three months of year 6). The trial is still ongoing.

The results of the RNS clinical trials show that responsive stimulation increases in effectiveness gradually. At the last follow-up, which was the beginning of year 6, the median reduction in seizure frequency was 65%. During the LTT, this percentage revolved around 60%, but some patients were seizure-free for a period of at least 1 year as well. In comparison, the 20 patients who had undergone open-loop stimulation suffered from at least 90% less seizures. This does not necessarily mean that open-loop is more effective than closed-loop. Most patients (9 out of 10) with a high seizure reduction during long-term treatment had simple partial motor seizures. It is likely that motor cortex responds differently to stimulation. The RNS trials were not powered to compare effectiveness between patients with different seizure foci, but at the end of the open-label phase of the Pivotal trial, the effectiveness of the treatment was similar between MTLE and non-MTLE patients. No data was presented on the effectiveness of treatment between patients with different neocortical seizure foci.

Another possible explanation of the seemingly more effective open-loop approach is that chronic stimulation suppresses tissue epileptogenicity and acts as a form of "medication", by providing continuous neuromodulation. Furthermore, the effects might be sustained. In both cases presented by (Valentin et al. 2015), reducing and terminating the stimulation did not result in immediate resurgence of EPC. It took several hours or even days for the positive effect of the treatment to vanish. (Valentín et al. 2016) reported that short-term stimulation (4-6 hours for four days) during intracranial monitoring resulted in seizure freedom for at least 20 months. Closed-loop stimulation does not provide the same continuous neuromodulation.

However, the mechanisms through which electrical stimulation interferes with epileptic seizures and interictal epileptiform activity are still unknown. There is also variability in the optimal stimulation parameters between patients. Some respond well to high-frequency stimulation, while low-frequency provokes seizures, in others it might be the reverse (Child et

al. 2014). This might be related to a plethora of factors, including exact seizure focus, its size, its connectivity patterns etc. Elucidating the mechanisms through which electrical stimulation modulates epileptiform activity in the brain would be greatly beneficial in determining the optimal parameters and approach for individual cases.

4.3. Practical considerations

From the viewpoint of practicality of each approach, several things should be considered. Firstly, the adverse effects must be minimal. The RNS clinical trials had a high percentage of implant site inflammation. This is understandable and expected, as the implantation procedure involves a long scalp incision and relatively large craniotomy to make place for the neurostimulator. The RNS battery is not rechargeable through the skin. This means that once it is depleted, the scalp should be opened again to replace the device. This puts the patient at risk every time a replacement is necessary. Another consideration for the RNS is that, as it is placed within the curvature of the skull, it is possible to cause damage to the underlying dura or the overlying scalp tissue. Even though such cases are not common, it is a risk to consider.

The Medtronic stimulator is not rechargeable either, but may be less invasive to replace, as the battery is implanted in the chest. However, this leads to another problem - the system includes wiring that goes around the neck towards the chest. This cable length is more easily susceptible to interference and the battery location can be inconvenient and less aesthetic.

Battery life is perhaps the most crucial technicality to consider, as it relates not only to the risks associated with reopening of the incisions, but also to interruption of treatment. On one hand, closed-loop stimulation can be more efficient in terms of preserving battery life. On the other hand, larger stimulation intensity is used in this modality (starting from 0.5 mA and above until tolerance). In contrast, (Velasco et al. 2009) used up to 450μA, i.e. just below the starting point of intensity which was used in the RNS trials (see Supplementary materials, Table 2). Since lower intensity means longer battery life, open-loop has the advantage if it decreases seizure frequency even at low amperage.

Another benefit of open-loop is that it does not require a detection algorithm. Within patients, epileptiform activity can manifest in different ways. It is hard to investigate the performance of such detection algorithms when continuous data recordings for months are not available. Long-term continuous ECoG recordings may reveal individual morphology during the pre-ictal and ictal period, and therefore help individual optimization of a detection algorithm (Freestone et al. 2015).

Moreover, it has been shown that less dense electrode grids are unable to detect microseizures, which can progress to large-scale seizures (Stead et al. 2010). In this train of thought, the effectiveness of open-loop stimulation does not depend on the detection of epileptiform activity.

One of the concerns regarding continuous stimulation is that it can potentially be damaging to the tissue. Charge density per phase (CDP) has been shown to be the critical variable to consider to avoid damage (McCreery et al. 1990). The articles reviewed here did not always specify whether CDP was within the safe margins. However, stimulation parameters were similar and therefore CDP must have been below the safe limit. In the open-loop paradigm the neuronal tissue receives much more stimulation in total, compared to closed-loop. Although side effects of the stimulation itself are not common, because the stimulation parameters are carefully optimized for each patient, it is preferable to keep the total exposure to electric stimuli to a minimum.

4.4. Perspective on CES for treatment of epilepsy

Around 30% of epilepsy patients cannot manage their seizures with AEDs. Many will not be candidates for resective surgery or laser ablation. Some have tried stimulation methods like VNS, but with limited effectiveness. Today, permanent implantation of electrodes and a neurostimulator is only an adjunctive therapy for epilepsy, alongside AEDs. The RNS clinical trials demonstrated that closed-loop stimulation can be beneficial in many patients and reduces seizure frequency. The five case reports on open-loop stimulation, which were discussed in this review, additionally demonstrate that responsive stimulation is not the only effective approach. No conclusions can be made yet on which one is better and both approaches seem promising.

Closed-loop stimulation can terminate detected seizure activity. Open-loop stimulation provides continuous neuromodulation, which seems to reduce the epileptogenicity of the cortex. To our knowledge, a combination of both approaches has never been tried before. A “hybrid” approach might both reduce seizures and IEDs, and manage seizures that do develop. The ideal result would be for medically intractable patients to discontinue AED treatment. AEDs can have side-effects which worsen the quality of life of the patient. Although stimulation methods are invasive and are usually less preferred than medication-only treatment, they are sometimes the only option for many patients. The “hybrid” approach might be a suitable replacement of AEDs, i.e. it is more effective and with less side effects. If

the risks related to implantation are minimized, a combination of open-loop and closed-loop stimulation could be a preferred method for treatment of medically intractable epilepsy.

The challenges that need to be addressed involve primarily the understanding of the mechanisms through which stimulation is beneficial for managing seizures (which would also help optimization of stimulation parameters), minimizing the risks associated with the invasiveness of the procedure, developing better and more efficient algorithms for seizure prediction. Since there is a great variability between patients in their responses to any modality of CES, it is possible that neither approach is the universally better one in all patients.

4.5. Further investigation of closed-loop versus open-loop

Further research should focus on optimizing stimulus parameters and responsive stimulation. Responsive stimulation was originally supposed to detect seizure susceptibility and stimulate upon the likelihood of seizure occurrence (Iasemidis et al. 2005). Current closed-loop algorithms do not estimate seizure likelihood and respond to this. (Cook et al. 2013) successfully conducted the first clinical trial of an invasive device dedicated to seizure prediction in 15 patients. (Good et al. 2009) applied in epileptic rats automated ‘just-in-time’ stimulation, which is similar to responsive stimulation, except that stimuli were not applied at seizure onset, but when a pathological pre-ictal synchronization was observed (which could be in the order of ten minutes before seizure onset).

Another method to identify seizure susceptibility is by applying TMS to probe cortical excitability. Cortical hyperexcitability is known as a marker for a pre-seizure state (Badawy et al. 2009). A simulation study by (Ehrens, Sritharan, and Sarma 2015) detected the transition from stable network mode to unstable mode using the firing rate of the most fragile node in the network. When this network was unstable, they applied a stimulus to stabilize it again. They were able to suppress seizures within 2 s after onset.

Computational models of epileptic network characteristics may provide alternative approaches to determine optimal stimulation parameters and the best location for stimulation. (Taylor et al. 2014) constructed a state space in which optimal stimulation is based on the amplitude and phase of a spike-wave cycle in spike-wave seizures. Their model proposes an adaptive approach to find optimal stimulation parameters individualized, based on real-time spike-wave detection. (Anderson et al. 2009) used a neural network simulation to study stimulation parameters and reported that the effect of stimulation is more effective when it is timed close to the negative ECoG peak of seizure activity. Same results were reported for

stopping after-discharges which occurred during electrical stimulation mapping (Motamedi et al. 2002).

Other improvements may be obtained in optimizing stimulus parameters in individuals. The current neuromodulation approaches apply periodic or responsive stimulations with individualized pre-determined stimulation parameters. (Chakravarthy, Tsakalis, et al. 2009) simulated different electrical stimulation-based control paradigms in which open-loop or closed-loop stimulation with an individualized pre-determined or adaptive stimulation was delivered. The adaptive stimulation outperformed all other paradigms for seizure control in this neural mass network (Chakravarthy, Sabesan, et al. 2009). Instead of determining the stimulus parameters prior to stimulation, adaptive stimulus parameters were determined by analysis of the network global state at the moment of stimulation (Tsakalis and Iasemidis 2006).

To be able to recommend to patients the optimal treatment modality, there must be a thorough understanding of each method. Responsive neurostimulation for epilepsy has been investigated in well-controlled clinical trials, while only five publications report on open-loop stimulation of neocortical seizure foci. This limits the study of the differences and similarities between closed-loop and open-loop in terms of effectiveness and adverse effects. Additional data needs to be collected. The following research questions can be addressed in future studies:

1. Does open-loop stimulation effectiveness differ from closed-loop?
2. Does the location of the seizure focus influence the effectiveness of the stimulation approach?
3. Does stimulation effectiveness depend on whether the seizure focus is on or near eloquent cortex?
4. What stimulation parameters are the most effective and safe?
5. Can neurostimulation potentially be used as an alternative to resective surgery or laser ablation?

Several factors and variables must be accounted for. First, it is necessary to investigate whether different neocortical seizure foci respond differentially to stimulation. This requires controlling for seizure focus location by including large samples of patients for as many different areas as possible. Another factor that might influence the effectiveness of stimulation is whether the seizure onset zone resides at or near eloquent cortex. Since eloquent cortex connectivity patterns have been proposed to be distinctive (Duffau, Moritz-Gasser, and

Mandonnet 2014), they might have a crucial effect on seizure propagation and, therefore, seizure termination.

A head-to-head adaptive randomized design can be employed to compare open-loop and closed-loop stimulation. However, it has some caveats. The first problem is technological - a device that is able to perform both kinds of treatment is required. Patients need to be randomly and blindly assigned to one of the two treatments at the time of enrolment in the study. This is necessary because the closed-loop approach involves a seizure detection algorithm, which needs to be optimized for each patient. If possible, the open-loop and closed-loop groups should be matched for seizure focus location. AEDs should be kept constant. Additionally, quality of life of patients should be evaluated using a standardized scale.

5. Conclusion

Electrical stimulation for epilepsy is a promising approach. Although the RNS System already has received market approval in the USA, the mechanisms of action of stimulation with respect to seizure reduction are largely unknown. Despite that, both the open-loop and closed-loop approaches have been shown to effectively and sustainably reduce seizure frequency in patients with medically intractable epilepsy. The two approaches have been investigated in different scales. Only twenty individual cases in which open-loop stimulation was used on neocortical seizure focus have been described. Yet, in most of them the reduction in seizure frequency is dramatic. However, closed-loop stimulation has also been largely effective in some cases. Both approaches are able to eliminate seizures for long period of time. Further research should focus on determining which approach, or combination of both, is the best option for patients with intractable epilepsy. More data needs to be collected in controlled double-blind studies. The potential of electrical stimulation in seizure management is considerable. If proper and optimal parameters and methods are developed, CES might even replace resective surgery or laser ablation in treating intractable epilepsy.

Conflict of interest

None

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Supplementary materials

Table 1. Selected publications with main study parameters and results.

	Study type	Number of patients	Seizure focus	Seizure frequency reduction	QOL (cognitive or non-cognitive)
Closed-loop					
Morrel, 2011 Heck et al., 2014	Pivotal trial (CT)	Start: 191 End: 174	Of all implanted patients (n = 256): MTLE – 43% (111) neocortical - 49.2% (126) mesial + neocortical - 7.4% (19)	(median) year 2: 55%	Yes - QOLIE scale
Bergey et al., 2015	LTT trial (CT)	Start: 230 End: 115		(median) year 6: 65%	Yes - QOLIE scale
Open-loop					
Elisevich et al., 2006	CR	1	Primary motor	Year 5: >90%	Yes - improvement of motor function
Velasco et al., 2009	CR	2	Case 1: SMA Case 2: primary motor	Case 1: month 18: 100% Case 2: month 18: 89%	Yes - QOLIE scale; reduction of aggressive behaviour
Child et al., 2014	CR	2	Case 1: primary motor Case 2: primary motor + language	Case 1: year 2: 100% Case 2: month 16: 99%	NA
Valentin et al., 2015	CR	2	Case 1: primary motor Case 2: primary motor	Case 1: month 22: >90% Case 2: month 22: >90%	Yes - improvement of motor function
Lundstrom et al. 2016	CR	13	Primary motor (2), Parietal cortex (3), Frontal cortex (2), temporal cortex (1), nonlesional (1), larger pathology (3)	>33-100%	Improvement in life satisfaction in 10 out of 13

Abbreviations: CT – clinical trial; CR – case report; MTLE – mesial temporal lobe epilepsy; SMA – supplementary motor area; QOL – quality of life; QOLIE – quality of life in epilepsy (scale)

Table 2. Stimulation parameters

	Frequency	Pulse width	Amplitude or voltage reported	CDP	Duration
Closed-loop (parameters are the same for both the Pivotal trial and the LTT trial)					
Morrel, 2011 Heck et al., 2014 Bergey et al., 2015	200Hz	160µs (burst duration: 100ms)	< 4mA in 53.8% of patients 4-7.9mA in 34.8% 8-11.9mA in 8.7% 12mA in 2.7%	NA	Total per day: mean 5.9 min/day; median 4.7 min/day; <7.3 min/day in 75% of patients
Open-loop					
Elisevich et al., 2006	50Hz	450µs	2.1mV	5.6µC/cm^2/phase charge per phase: 0.67 µC/phase	Cyclic (3 min ON, 10 min OFF)
Velasco et al., 2009	130Hz	450µs	< 450µA	3.0µC/cm^2/phase	Case 1: continuous (11 months for patient 1); cyclic (1 min ON, 4 min OFF) (7 months) Case 2: cyclic (1 min ON, 4 min OFF)
Child et al., 2014	100Hz	120ms	Case 1: 7.0V Case 2: 3.5V	NA	Continuous
Valentin et al., 2015	60–130Hz	450µs	3mA	NA	Continuous
Lundstrom et al. 2016	2-100Hz	90-450µs	1-6V	NA	Continuous

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