Neurostimulation as a promising epilepsy therapy

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Epilepsia Open, 2(4):371–387, 2017
doi: 10.1002/epi4.12070

SUMMARY

The revolution in theory, swift technological developments, and invention of new devices have driven tremendous progress in neurostimulation as a third-line treatment for epilepsy. Over the past decades, neurostimulation took its place in the field of epilepsy as an advanced treatment technique and opened up a new world. Numerous animal studies have proven the physical efficacy of stimulation of the brain and peripheral nerves. Based on this optimistic fundamental research, new advanced techniques are being explored in clinical practice. Over the past century, drawing on the benefits brought about by vagus nerve stimulation for the treatment of epilepsy, various new neurostimulation modalities have been developed to control seizures. Clinical studies including case reports, case series, and clinical trials have been booming in the past several years. This article gives a comprehensive review of most of these clinical studies. In addition to highlighting the advantages of neurostimulation for the treatment of epilepsy, concerns with this modality and future development directions are also discussed. The biggest advantage of neurostimulation over pharmacological treatments for epilepsy is the modulation of the epilepsy network by delivering stimuli at a specific target or the “hub.” Conversely, however, a lack of knowledge of epilepsy networks and the mechanisms of neurostimulation may hinder further development. Therefore, theoretical research on the mechanism of epileptogenesis and epilepsy networks is needed in the future. Within the multiple modalities of neuromodulation, the final choice should be made after full discussion with a multidisciplinary team at a presurgical conference. Furthermore, the establishment of a neurostimulation system with standardized parameters and rigorous guidelines is another important issue. To achieve this goal, a worldwide collaboration of epilepsy centers is also suggested in the future.

KEY WORDS: Vagus nerve stimulation, Deep brain stimulation, Responsive neurostimulation system, Repetitive transcranial magnetic stimulation, Transcranial direct current stimulation.

Epilepsy, a common neurological disease, imposes significant psychological, physical, and financial burdens on patients and their families. A study on outcomes of antiepileptic drug therapy in newly diagnosed epilepsy showed that 25% of patients never achieved seizure freedom. For patients with drug-resistant epilepsy, only a small proportion are good surgical candidates. The treatment of patients who are not eligible for surgery or continue to have seizures after surgery is still a major challenge. Over the past several decades, one of the most impressive achievements in epilepsy treatment is neurostimulation therapy, which has been heavily researched and developed. Over the next couple of years, it is estimated that new invasive and noninvasive neurostimulation techniques will progress dramatically. An “era of neurostimulation” is coming.

Comprehensive progress in principles, techniques, and devices advances neurostimulation as a novel and successful therapeutic tool for treating epilepsy. The research on
Electrophysiology and the theory of epilepsy networks have made useful contributions to a better understanding of epilepsy. Animal research has shown the potential antiepileptic effect of stimulation on deep nuclei, cerebella, cortex, and peripheral nerves. Insights gained from this fundamental research drove further hypotheses and led to new experimental designs and trials in humans. Modern technologies such as stereotaxy and robotics in deep brain stimulation (DBS) systems, detection of abnormal electrocorticogram activity in responsive neurostimulation (RNS) systems, and infrared navigation and special H-coil in repetitive transcranial magnetic stimulation (rTMS) systems are making their way forward quickly. At the present time, several devices have been invented and applied in epilepsy treatment (Table 1). Vagus nerve stimulation (VNS) and RNS have gained U.S. Food and Drug Administration (FDA) approval for the treatment of epilepsy, and DBS of the anterior nucleus of thalamus (ANT) has approval from the European Medicinal Agency. Other neurostimulation modalities, such as rTMS and transcranial direct current stimulation (tDCS), are also under investigation and have shown encouraging results.

The current article focuses on discussing the results of clinical trials for each neurostimulation modality, comparing the differences, and delineating the patient groups that may benefit most from each. We also discuss challenges and potential future developments in this field. Although numerous studies have been published, large-scale, well-designed clinical trials are limited. Seizure type, target, parameters, and follow-up vary among these trials, case series, and case reports. It is probably not objective to draw a final conclusion for the performance of neurostimulation at this stage. However, neurostimulation is undoubtedly becoming a promising therapeutic option for epilepsy and shows favorable results.

### VNS

VNS was approved in the United States in 1997 for adjunctive therapy of patients 12 years or older with refractory focal seizures. A report in 1972 showed that over 85,000 epilepsy patients had VNS devices implanted. In this procedure, a neurocybernetic prosthesis is implanted under the skin of the chest. The stimulating electrodes carry intermittent electrical currents from the generator to the vagus nerve, according to adjusted preprogrammed settings. Stimulation activates brainstem nuclei, from which widespread projections reach the limbic, reticular, and autonomic regions of the brain, which may influence norepinephrine levels in potential epileptogenic regions.

Table 1. Devices of neurostimulation

| Neurostimulation technique | Devices |
|---------------------------|---------|
| VNS | Implantable VNS therapy system (the NeuroCybernetic Prosthesis System) |
| | NEMOS transcatheter VNS |
| | AspireSR generator |
| | Medtronic DBS leads (Medtronic, Minneapolis, MN, U.S.A.) |
| | Modified Resume 4-button electrodes (Medtronic) |
| | Electrodes & transmitters (Avery Laboratories, Farmingdale, NY, U.S.A.) |
| DBS | The RNS System (NeuroPace) |
| | Magnetic stimulator (Magstim Super-Rapid; Magstim Co., Whitland, United Kingdom) |
| | Dantec stimulator (Medtronic) |
| | Cadwell rapid-rate magnetic stimulator (Cadwell Laboratories, Kennewick, WA, U.S.A.) |
| | Nicolet Endeavor CR (VIASYS Healthcare, U.S.A.) & disposable stainless-steel subdermal needle (Cardinal Health, U.S.A.) |
| | Stimulator (Schneider Electronic, Giechen, Germany) |
| | Stimulator (Magstim Eldith DCS) |
| | Phoresor II Auto Model PM850 (IOMED, Salt Lake City, UT, U.S.A.) |
| | Stimulator (Soterix Medical, Model 1224-B, New York, NY, U.S.A.) |
| | Stimulator (Chattanooga Intelect Advanced Combo) |

rTMS, repetitive transcranial magnetic stimulation; tDCS, transcranial direct current stimulation; VNS, vagus nerve stimulation.
epileptogenic state.\(^{11}\) A recent VNS study on pediatric intractable epilepsy patients showed >50% seizure frequency reduction was achieved in 9.8% (6th month), 24% (2nd year), 46.4% (3rd year), 54% (5th year), and 62.5% (last follow-up in 5th year).\(^{12}\) Another study examined 5,554 patients from the VNS therapy Patient Outcome Registry and found that 49% of patients had >50% seizure frequency reduction, with 5.1% becoming seizure free 4 months after implantation, whereas 63% of patients had >50% seizure frequency reduction, with 8.2% seizure free at 24–48 months.\(^{13}\) However, the long-term effects of VNS should be interpreted carefully due to the uncontrolled data in these trials and the potential natural history of drug-resistant epilepsy.\(^{14,15}\) A 2015 Cochrane analysis reviewed the evidence for the efficacy and tolerability of VNS based on four short-duration trials.\(^{16}\) Results showed that >50% seizure frequency reduction occurred in 40% of patients for the entire study group, and VNS using the high-stimulation paradigm was significantly better than low stimulation in reducing seizure frequency. The common adverse events included hoarseness, cough, dyspnea, paresthesia, headache, pain, and nausea.\(^{17}\) Most adverse effects resolved after 1 year of continued treatment. Overall, VNS is well tolerated, and complications are relatively uncommon and minor.

As the earliest neurostimulation technique approved in clinical practice, VNS has been used worldwide in epilepsy centers as an efficient treatment for drug-resistant epilepsy. It provides treatment for both focal and generalized seizures, for both children and adults, and for mood problems in adults with epilepsy. VNS may have improved efficacy over time. The surgical procedure takes approximately 2 h and is technically less complicated than DBS surgery. After implantation, 1 or 2 years of frequent visits to the outpatient clinic are needed for adjusting stimulation paradigms. The stimulator battery lasts 2.8–8.2 years, depending on the settings used.\(^{18}\) Approximately one-half of patients required at least one type of battery replacement or revision surgery. The most common surgeries were for generator battery depletion, poor efficacy, and lead malfunction.\(^{19}\) VNS device and lead implantation cost about $25,000–$30,000.\(^{20}\) It is unaffordable in some developing countries, which limits its application.

Transcutaneous VNS (tVNS) is a noninvasive technique intended to have similar effects as implanted VNS. It stimulates the auricular skin branch of the vagus nerve. Aihua et al. studied 47 patients with tVNS applied bilaterally and found that in the stimulation group the monthly seizure frequency decrease compared with baseline after 12 months (\(p < 0.001\)). In the stimulation group, the seizure frequency was lower than in the control group after 12 months (\(p < 0.001\)). Mood status also improved in the treatment group.\(^{21}\) Another study enrolled 144 patients with refractory focal seizures, and all of the patients were treated with unilateral tVNS for 24 weeks. After 8 weeks, the percentage seizure frequency reduction was 42.6% in the stimulation group and 11.5% in the control group. After 24 weeks, patients in the stimulation group had a seizure frequency reduction of 47.7%. The patients in the control group were switched into stimulation after 8 weeks of treatment. After an additional 16 weeks, these patients had a seizure frequency reduction of 47.5%.\(^{22}\) Although the reports are limited, the results are encouraging. The tVNS device costs much less than the implanted VNS device, and may provide bilateral stimulation that patients tolerate well, but the efficacy needs further investigation.

Recently, a new VNS device was approved in Europe. The stimulator is able to detect a predetermined pattern and magnitude of heart rate increase and automatically deliver an additional stimulus if the heart rate increase exceeds a given threshold. A case report showed that the additional VNS stimulation could reduce seizure duration significantly, which might provide potential protection for patients from the harm of prolonged seizures.\(^{23}\)

**DBS**

Different from VNS, DBS can aim at specific anatomical brain targets such as ANT,\(^{24,25}\) centromedian thalamic nucleus (CM),\(^{24,27,39-44}\) subthalamic nucleus (STN),\(^{36,45-49}\) caudate nucleus,\(^{50}\) cerebellum,\(^{51-58}\) and hippocampus (Table 2).\(^{59-73}\) The ANT is the most promising target for its rich connectivity with limbic system through the fornix and mammillothalamic tract.\(^{26}\) DBS with a target of the ANT has been approved in Europe for treatment of focal epilepsy in adult patients 18–65 years old and is waiting for approval in the United States by the FDA. Supportive evidence was found in a U.S. multicenter double-blind randomized controlled trial (Stimulation of the Anterior Nucleus of the Thalamus for Epilepsy [SANTE]), which enrolled 110 patients with refractory focal epilepsy.\(^{26}\) More than half of them had previous epilepsy surgery or VNS implantation. The patients enrolled had relatively high seizure frequency, which varied from six times per month to 10 times per day. The high-frequency stimulations (>100 Hz) were given bilaterally to the ANT using a transventricular approach. At the end of the blinded phase, the seizure frequency reduction was 40.4% in the stimulation group and 14.5% in the control group. The median seizure frequency decreased 56% from baseline by the end of 2 years and to 69% by the end of 5 years.\(^{29}\) It also showed that temporal epilepsies benefited more compared to those with seizures arising from other lobes or multifocal regions. This might be attributed to rich connectivity of the ANT with the limbic system via the Papez circuit. The patients’ quality of life also improved in long-term follow-up. None of the subjects had brain infections or symptomatic hemorrhage in this trial. Device implantation or stimulation-related complications primarily included implant site pain (20.9%) and paresthesia (22.7%). Nearly 15% of the subjects reported

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**Epilepsia Open** 2(4):371–387, 2017
doi: 10.1002/epi4.12070
## Table 2. Summary of clinical data using DBS in epilepsy

| Target | Reference | No. of pts | Design of study | Seizure type | Stimulation parameters | Follow-up, mo | Results | Adverse events |
|--------|-----------|------------|-----------------|--------------|------------------------|---------------|---------|----------------|
| ANT    | Valentín (2017) | 1          | Open-label     | Focal onset  | NR                     | 12            | >60% SR | Increased aggression |
| ANT    | Krishna (2016)  | 16         | Open-label     | Generalized & focal onset | 100–185 Hz, 2.4–7 V, 90 µs, 1 min on/5 min off | 14–153 | 11.5% median SR |
| ANT    | Lehtimäki (2016) | 15         | Open-label     | Focal onset  | 140 Hz, 5 V, 90 µs, 1 min on/5 min off | 25.2 (9–52) | 69% RR |
| ANT    | Salanova (SANTE; 2015) | 83        | Double-blind randomized controlled | Focal onset | 145 Hz, 5 V, 90 µs, 1 min on/5 min off | 61 | 69% median SR |
| ANT    | Piacentino (2015) | 6          | Open-label     | Focal onset  | 130–140 Hz, 4 V, 90 µs | 12–48 | 33–80% SR |
| ANT    | Oh (2012) | 9          | Open-label     | Focal onset  | 100–185 Hz, 1.5–3.1 V, 90–150 µs, continuous | 34.6 (22–60) | 57.9% median SR |
| ANT    | Lee (2012) | 15         | Open-label     | Generalized & focal onset | 100–185 Hz, 1.5–3.1 V, 90–150 µs, continuous | 39 (24–67) | 70.5% median SR |
| ANT    | Andrade (2010) | 2          | Open-label     | Dravet syndrome | NR                     | 120 | 67–98% SR |
| ANT    | Fisher (SANTE; 2010) | 110      | Double-blind randomized controlled | Focal onset | 145 Hz, 5 V, 90 µs, 1 min on/5 min off | 24 | 56% median SR |
| ANT    | Osorio (2007) | 4          | Open-label     | MTLE         | 175 Hz, 4.1 V, 90 µs | 36 | 53.4–92.8% SR |
| ANT    | Lim (2007, 2008) | 4          | Open-label     | Generalized & focal onset | 90–100 Hz, 4–5 V, 60–90 µs | 24 | 35–76% SR |
| ANT    | Andrade (2006) | 6          | Open-label     | Generalized & focal onset | 100–185 Hz, 1–10 V, 90–120 µs, 1 min on/5 min off | 60 | 100% RR |
| ANT    | Lee (2006) | 3          | Open-label     | Focal onset  | 130 Hz, 90 µs, 1 min on/5 min off, alternating left–right | 15–450 | 75.4% median SR |
| ANT    | Kerrigan (2004) | 5          | Open-label     | Focal onset  | 100 Hz, 1–10 V, 90 µs, 1 min on/10 min off, alternating left–right | 20.4 (6–36) | 80% RR of injurious seizures |
| ANT    | Hodisie (2002) | 5          | Open-label     | Generalized & focal onset | 100 Hz, 10 V, 90 µs, 1 min on/5 min off, alternating left–right | 14.9 (10.6–20.7) | 24–89% SR |

Continued
| Target | Reference            | No. of pts | Design of study | Seizure type | Stimulation parameters | Follow-up, mo | Results | Adverse events |
|--------|----------------------|------------|----------------|--------------|------------------------|---------------|---------|----------------|
| CM     | Valentin (2017)²⁷      | 2          | Open-label     | Generalized  | NR                     | 18-48         | ≥60% SR (1 pt) | No improvement (1 pt) |
| CM     | Sun (2016)⁴¹          | 14         | Open-label     | Generalized & focal onset | 120-130 Hz, 0-2.6 V, 90-150 µs | 18 | 68% median SR | 100% RR (LGS) |
| CM     | Valentin (2013)⁴⁴     | 11         | Single-blind controlled | Generalized & focal onset | 60-130 Hz, <5 V, 90 µs, bilateral | 24 (12-66) | 83% RR (generalized) | 20% RR (focal onset) |
| CM     | Cukiert (2009)⁴³      | 4          | Open-label     | Generalized  | 130 Hz, 2 V, 300 µs, bilateral | 18 (12-24) | 65-98% SR | Increased attention |
| CM     | Velasco (2006)³⁹      | 13         | Open-label     | LGS          | 130 Hz, 400-600 µA, 450 µs | 46 (23-132) | 80% SR | Skin erosion (2 pts) |
| CM     | Andrade (2006)²⁴      | 2          | Open-label     | Generalized & focal onset | 100-185 Hz, 1-10 V, 90-120 µs, 1 min on/4 or 5 min off | 24-84 | No improvement | Intermittent nystagmus (1 pt) |
| CM     | Velasco (2000)⁴⁰      | 13         | Double-blind controlled | Generalized & focal onset | 60 Hz, 4-6 V, 1 min on/4 or 5 min off, alternating left-right | 41.2 (12-94) | 81.6% median SR (LGS) | 57.3% median SR (s GTCS) |
| CM     | Fisher (1992)⁴²       | 7          | Double-blind crossover | Generalized | 65 Hz, 0.5-10 Hz, 90 µs, 1 min on/4 off, bilateral 2 h/day | 12-22 | 30% median SR (GTCS) | 50% RR (stimulation 24 h/day) |
| STN    | Capecci (2012)⁴⁹      | 2          | Open-label     | Generalized & focal onset | 130 Hz, 0-5 V, 90 µs, bilateral, continuous | 18-48 | Pt 1: 65% SR (focal motor) & 100% SR (GTCS) | Pt 2: no improvement & an increase of stimulation-associated atypical absence rate |
| STN    | Vesper (2007)⁴⁸       | 1          | Open-label     | PME          | 130 Hz, 3 V, 60-120 µs, bilateral | 12 | 50% SR | |
| STN    | Lee (2006)³⁶          | 3          | Open-label     | Focal onset  | 5-10 Hz, 3-7 V, 90 µs | 1-30 | 49.1% median SR | 33-50% SR |
| STN    | Handforth (2006)⁵⁵    | 2          | Open-label     | Focal onset  | 130-185 Hz, <3.5 V, 60-90 µs, bilateral | 26-32 | |
| STN    | Shon (2005)⁴⁷         | 2          | Open-label     | Focal onset  | 130 Hz, 60-90 µs | 6-18 | 86.7-88.6% SR | |
| STN    | Chabardès (2002)⁵⁶    | 5          | Open-label     | Focal onset, Dravet syndrome, & ADHLE | 130 Hz, 1.5-5.2 V, 90 µs, continuous | 10-30 | 67-80.7% SR (3 pts) | 41.5% in Dravet syndrome |
| STN    | Velasco (2005)⁴⁴      | 5          | Double-blind randomized controlled | Generalized | 2 µC/cm²/phase, 10-20 Hz, 3.8 mA, 2.28 V, 450 µs | 10-48 | 76% median SR (GTCS) | Infection (1 pt) |

**Cerebellum**

| Target | Reference            | No. of pts | Design of study | Seizure type | Stimulation parameters | Follow-up, mo | Results | Adverse events |
|--------|----------------------|------------|----------------|--------------|------------------------|---------------|---------|----------------|

| Cerebellum | Velasco (2005)⁵¹ | 5 | Double-blind randomized controlled | Generalized | 2 µC/cm²/phase, 10-20 Hz, 3.8 mA, 2.28 V, 450 µs | 10-48 | 76% median SR (GTCS) | Infection (1 pt) |

**Continued**
| Target          | Reference             | No. of pts | Design of study | Seizure type                     | Stimulation parameters                                                                 | Follow-up, mo | Results                                                                 | Adverse events                                                 |
|-----------------|-----------------------|------------|-----------------|----------------------------------|----------------------------------------------------------------------------------------|---------------|-------------------------------------------------------------------------|------------------------------------------------------------------|
| Cerebellum      | Davis (1992)          | 27         | Open-label      | Heterogenous                     | 0.8–2.5 μC/cm²/phase, 150–180 Hz, 0.5–1.4 mA, 2.28 V, 500 μs                            | 24–204        | 44% SF                                                                  | Wound infection (2 pts)                                         |
| Cerebellum      | Wright (1984)         | 12         | Double-blind    | Generalized & focal onset        | 10 Hz, 1–7 mA                                                                        | 6             | No significant improvement                                              | Mechanical failed (1 pt)                                         |
| Cerebellum      | Levy (1979)           | 6          | Open-label      | Generalized & focal onset        | 10 Hz, 2.25–8 V, alternating left–right                                               | 7–20          | 27–100% SR (3 pts)                                                      | Wound infection (2 pts)                                         |
| Cerebellum      | Van Buren (1978)      | 5          | Double-blind    | Generalized & focal onset        | 10–14 V, 10 & 200 Hz, alternating left–right                                          | 24–29         | No improvement                                                          | Skin erosion (1 pt)                                             |
| Cerebellum      | Cooper (1978)         | 29         | Open-label      | Focal onset                      | 10 & 200 Hz                                                                           | 25            | 62% pts with clinically significant improvement                          | Development of kindling phenomenon                               |
| Cerebellum      | Sramka (1976)         | 3          | Open-label      | Generalized & focal onset        | 10 & 100 Hz, 10 V, 1,000 μs                                                          | 0             | 100% temporary improvement                                              | Development of kindling phenomenon                               |
| Cerebellum      | Cooper (1976)         | 15         | Open-label      | Generalized & focal onset        | 10 Hz, 10 V                                                                           | 11–38         | 73% pts with clinical improvement                                       | Development of kindling phenomenon                               |
| Hippocampus     | Lim (2016)            | 71         | Open-label      | MTLE                             | 5 or 145 Hz, 1 V, 90–150 μs, unilateral, bilateral                                     | 38.4 (30–42) | 45% median SR                                                            |                                                                  |
| Hippocampus     | Jin (2016)            | 72         | Open-label      | MTLE                             | 130–170 Hz, >3.5 V, 450 μs, unilateral, bilateral                                     | 34.7 (26–43) | 93% median SR                                                            |                                                                  |
| Hippocampus     | Cukiert (2014)        | 73         | Open-label      | Temporal epilepsy                | 130 Hz, 1–3.5 V, 300 μs, unilateral (78%) bilateral (22%)                            | 30.1          | 61% median SR, 78% RR                                                    |                                                                  |
| Hippocampus     | Vonck (2013)          | 74         | Open-label      | MTLE                             | 130 Hz, 1–3.1 V, 450 μs, unilateral, bilateral                                        | 96 (67–120)  | 70% median SR, 80% RR                                                    |                                                                  |
| Hippocampus     | Bondallaz (2013)      | 75         | Open-label      | MTLE                             | 130 Hz, 0.5–2 V, 450 μs, unilateral, bilateral                                        | 18            | 67% median SR, 75% RR                                                    |                                                                  |
| Hippocampus     | Min (2013)            | 76         | Open-label      | MTLE                             | 130 Hz, 2.6–3.6 V, 450 μs, 60 s on/off                                          | 18–36         | 65–90% SR                                                               |                                                                  |
| Hippocampus     | Tyrand (2012)         | 77         | Open-label      | Temporal epilepsy                | 130 Hz, 1 V, 210–450 μs                                                             | 0             | 58.1% reduction of interictal activity with biphasic stimulation in HS  |                                                                  |
| Hippocampus     | Boëx (2011)           | 78         | Open-label      | MTLE                             | 130 Hz, 0.5–2 V, 450 μs, unilateral, continuous                                        | 43.5 (12–74) | 75% RR                                                                  | Lead displacement (1 pt)                                        |
| Hippocampus     | McLachlan (2010)      | 79         | Double-blind randomized controlled crossover | Temporal epilepsy                | 185 Hz, 90 μs, unilateral                                                            | 3             | 33% median SR                                                            | Reversible memory impairment (2 pts)                             |
| Target       | Reference          | No. of pts | Design of study | Seizure type              | Stimulation parameters                                      | Follow-up, mo | Results | Adverse events                                      |
|--------------|--------------------|------------|-----------------|---------------------------|-----------------------------------------------------------|----------------|---------|----------------------------------------------------|
| Hippocampus  | Boon (2007)        | 10         | Open-label      | Temporal lobe onset       | 130–200 Hz, 2–3 V, 450 μA, unilateral, bilateral          | 31 (15–52)    | 70% RR | Asymptomatic ICH (1 pt)                              |
| Hippocampus  | Velasco (2007)     | 9          | Double-blind    | MTLE                      | 130 Hz, 300 μA, 450 μs, 1 min on/4 min off, bilateral 20%, unilateral 80% | 18             | 55% RR | Skin erosion & implant site infection (3 pts)         |
| Hippocampus  | Tellez-Zenteno (2006) | 4         | Double-blind randomized controlled multiple crossover MTLE | 190 Hz, 90 μs             | 6              | 15% SR |                                                    |
| Hippocampus  | Vonck (2005)       | 7          | Open-label      | Temporal onset            | Unilateral                                               | 14 (5.5–21)    | 57% RR |                                                    |
| Hippocampus  | Vonck (2002)       | 3          | Open-label      | Temporal onset            | 130–200 Hz, 1.0 V, 450 μs, unilateral                     | 5 (3–6)        | 100% RR | 77% median SR                                      |
| Hippocampus  | Velasco (2000)     | 10         | Open-label      | Bilateral temporal onset  | 130 Hz, 200–400 μA, 450 μs, bilateral 20%, unilateral 80% | 0.5            | 70% SF |                                                    |

DBS, deep brain stimulation; pt(s), patient(s); ANT, anterior nucleus of thalamus; NR, not reported; SR, seizure reduction; RR, responder (seizure reduction >50%) rate; SANTE, stimulation of the anterior nucleus of the thalamus for epilepsy; TLE, temporal lobe epilepsy; FLE, frontal lobe epilepsy; SUDEP, sudden unexpected death in epilepsy; MTLE, mesial temporal lobe epilepsy; ICH, intracranial hemorrhage; CM, centromedian thalamic; LGS, Lennox-Gastaut syndrome; sGTCS, secondary generalized tonic-clonic seizures; GTCS, generalized tonic-clonic seizures; STN, subthalamic nucleus; PME, progressive myoclonic epilepsy; ADFLE, autosomal dominant frontal lobe epilepsy; SF, seizure freedom; CSF, cerebral spinal fluid.
depression, and 6.4% reported memory problems as adverse events. Other studies also showed promising results, with most seizure reductions >50%. However, an insertional effect after the implantation could not be excluded due to the open-label designs. A recent study from Finland further investigated ANT as the optimal target for DBS and found that stimulation in the anterior region of ANT had the best therapy response. 

In addition to ANT stimulation, other targets were also investigated. Cerebellar stimulation has been used for >50 years but has had conflicting results. The proposed theory of cerebellar stimulation was that stimulation of the Purkinje cells might intensify the inhibitory cerebellar output to the thalamic neuronal network and subsequently inhibit its excitatory output to the cerebral cortex. To date, there have been three clinical double-blind studies, with similar stimulus parameters but completely contradictory results. Two of them failed to show any significant seizure reduction whereas the third showed seizure reduction up to 57–76%. The exact stimulation target in the cerebellum and certain seizure patterns might be responsible for these differences in findings. Wound infection was a commonly occurring complication. The existing clinical data suggest that cerebellar stimulation remains a target worth exploring for defining its potential benefit in the treatment of epilepsy.

Hippocampus DBS is a valuable option for patients with drug-resistant mesial temporal lobe epilepsy (MTLE) in whom surgery is contraindicated. Three double-blind studies showed 15–33% seizure reduction and 55% responder rate whereas other open-label studies showed 45–93% seizure reduction and 57–100% responder rate. Velasco et al. found hippocampus stimulation to be significantly more effective in magnetic resonance imaging (MRI)-negative patients. It was speculated that the neuronal network needed to be preserved in the stimulated site to achieve a good response to stimulation, and severe neuronal reduction in sclerotic tissue represented a poor tissue for modulation with stimulation. Tyrand et al. found that biphasic stimuli are more efficient than pseudomonophasic pulses in patients with hippocampal sclerosis (HS), probably related to an enlargement of the stimulated fiber populations. Vonck et al. noted that bilateral rather than unilateral stimulation might have superior efficacy in unilateral mesial temporal epilepsy. Lim et al. demonstrated that low-frequency stimulation was tolerable and reduced the frequency of seizures in long-term follow-up in patients with HS. However, Boëx et al. described the beneficial effect of high-frequency stimulation but not low-frequency stimulation in MRI-negative MTLE. They also speculated that the efficiency of stimulation in MRI-negative MTLE might be linked to the correlation between the localization of the epileptogenic zone and of the electrode. Another study suggested that a decrease in epileptiform discharges by stimulation in drug-resistant MTLE seemed not to be directly associated with the location of the electrode relative to the epileptogenic zone. Therefore, better understanding of the mechanism by which DBS suppresses seizures, optimization of stimulus parameters, and identifying the exact targets are still required. Overall, the complications associated with hippocampus DBS were less than with other DBS targets, although reversible worsening of memory function might occur.

CM is another potential target. More than 60 patients treated using CM stimulation and reported to date have provided evidence that CM stimulation was most effective in generalized epilepsies, particularly in Lennox–Gastaut syndrome, for its diffuse projections to the striatum and cerebral motor cortex and role in gatekeeping and rhythm-generating activities. Two double-blind, one single-blind, and several open-label studies showed 30–98% seizure reduction and 50–100% responder rate for generalized epilepsy and 20–70% responder rate for focal onset epilepsy. Skin infection was a frequent complication.

The effect of STN stimulation is still doubtful. The limited studies are all open-label and have small sample sizes, with approximately 50% median seizure reduction. Accurate placement of DBS electrodes is an important but not an easy task. In the SANTE trial, 8.2% of patients had misplaced DBS electrodes located outside the ANT. Driving response (DR) is a rhythmic cortical electroencephalographic (EEG) synchronization elicited by low-frequency stimulation of the thalamus and has been regarded as an indirect indicator that helps locate the electrode contact within the thalamus. However, the localization value of DR as a predictor of correct electrode placement within the thalamus is still controversial.

Son et al. investigated the relationship between DR and the location of 11 electrodes in six epilepsy patients with ANT DBS and found DR could be observed in one misplaced electrode (within the third ventricle). They concluded that DR could be regarded as misplaced if it was not elicited, but it could not be interpreted as a sound indicator of correct placement if DR is elicited. Zumsteg et al. found no differences in this EEG synchronization phenomenon between stimulation of the ANT and dorsomedial nucleus, and considered it as a mixed activation of both specific and non-specific thalamocortical pathways. Therefore, the localizing value of DR is still limited, and its prediction of clinical efficacy is questionable and needs to be clarified in the future.

Except for the initial electrode localization during procedure, electrode migration during follow-up is another common technique issue. Unplanned migration of a DBS electrode after placement at the intended target can lead to a
poor surgical outcome and added cost. The percentage of
electrode migrations was reported to be 0.94–2.5% in move-
ment disorder populations, which is less than that found in
epilepsy patients who underwent DBS.29,83–86 The reason
for this difference is unclear, but may be associated with dif-
fferences in the target selection. Some new techniques, such
as microtextured surfaces, are being developed to minimize
the migration of the DBS lead.87 Additionally, regular
follow-up imaging and postoperative care are also war-
ranted in DBS patients.

In conclusion, DBS provides a safe and effective option
for refractory focal epilepsy with or without secondarily
generalized tonic–clonic seizures. The patients with sei-
zure arising from the temporal lobe benefit the most (up to
76% in the SANTE study) from DBS at ANT due to the
involvement of ANT in the limbic system. The efficacy of
DBS from the available data is slightly higher than VNS.
However, the application of DBS is relatively limited, and
debates about the optimal approach to the ANT and optimal
target are still ongoing. DBS is in general a more elaborate
and complication-prone procedure, requiring a well-trained
team of qualified stereotactic neurosurgeons and neurolo-
gists. The complications of DBS are potentially more
numerous and serious (up to 34% in the SANTE study)
compared to VNS. The cost is higher for DBS, because the
device is more expensive and the operating time is longer.
From the data regarding DBS in movement disorders, the
DBS device and lead implantation cost about $29,000–
$34,000, which is more costly than VNS.88,89 Similar to
VNS, DBS also requires periodic follow-up visits to verify
correct functioning and optimal parameter settings, and the
stimulators must be replaced when the batteries are
depleted. The stimulator battery usually lasts 4–7 years,
depending on the settings used.

**RNS System**

Both VNS and DBS are open-loop stimulation systems,
which control seizures by modulating the activity of certain
hubs of the epilepsy network continuously. In contrast, the
RNS system is the first closed-loop stimulation system that
works via delivering electrical pulses when a seizure is
detected. It is well known that electrical activity spreads
monosynaptically and polysynaptically from a local region
to other regions in focal onset epilepsy. The RNS system
was designed to identify the critical region or propagation
pathways and to provide disruption. In 2013, the RNS sys-
tem acquired FDA approval for the treatment of adult
(18 years or older) focal onset refractory epilepsy (refrac-
tory to two or more antiepileptic drugs) with frequent and
disabling focal onset seizures localized to no more than two
epileptogenic foci. In this system, one or two electrodes,
which are placed at seizure foci, not only monitor EEG con-
tinuously but also deliver an electric current once the seizure
is detected. Clinicians have modified parameters, such as
area tool, line length tool, and half wave tool, to optimize
the sensitivity and specificity of detecting seizures individu-
ally. When these tools detect abnormal EEG activity, a
biphasic electric stimulus is given between two of the elec-
trodes or between one electrode and the neurostimulator
case. The electrical stimulation effects may be attributed to
depolarization blockade, synaptic inhibition, and pathologic
network modulation.90 In a multicenter double-blind ran-
domized controlled trial, 191 patients with refractory focal
seizures with baseline seizure frequency of ≥3 disabling sei-
zures per month were enrolled and had an RNS system
implanted. Electrodes were implanted at one or two located
seizure foci and connected to a sensor–stimulator device.
At the end of a 12-week blinded phase, seizure frequency
decreased 37.9% in the stimulation group versus 17.3% in
the control group. The therapeutic effect appeared sustained
over time. The seizure frequency reduction was 44% after
1 year and 53% after 2 years. The percentage of patients
with >50% seizure frequency reduction was also 44% after
1 year and 55% after 2 years. There were significant
improvements in quality of life. Implant site infection
occurred in five subjects (2.6%), and intracranial hemor-
rhage occurred in four subjects (2.1%). The patients toler-
ated RNS well, with no deterioration in mood or
neuropsychological function.91–93 In an ongoing 7-year
multicenter prospective open-label study, the median sei-
zure frequency reduction went from 48% to 66% over
postimplant years 3 through 6. The improvements in quality
of life were maintained. Implant site infection (9.0%) was
the most common adverse events over the mean 5.4 years
of follow-up (Table 3).94

RNS provides another promising treatment for focal epi-
lepsy patients, especially those with bitemporal epilepsy or
epilepsy arising from eloquent regions. Compared to open-
loop stimulation, RNS has a longer battery life due to the
lower stimulation dose. Additionally, the stimulation is
restricted to one or two seizure foci and does not disrupt nor-
mal brain function, thus resulting in fewer adverse events.
For optimal treatment effects, a precise localization of sei-
zure foci is a prerequisite. RNS candidates are always those
who are not suitable for surgery and who have had seizures
localized to one or two foci. The initial and limited reports
efficacy of RNS are promising. Further studies regarding
optimization of seizure detection techniques and stimulation
paradigms are encouraged to achieve maximum efficiency.

**External Trigeminal Nerve Stimulation**

External trigeminal nerve stimulation (eTNS) is a nonin-
vasive treatment for epilepsy that has been used in Europe,
Canada, and Australia and is investigational in the United
States.95 The mechanism of eTNS treatment is similar to
that of VNS, but the electrodes are placed noninvasively on
both sides of forehead. It provides bilateral stimulation of
the supraorbital nerves. In a randomized controlled trial, DeGiorgio et al.\textsuperscript{96} studied 50 patients with refractory epilepsy. After an 18-week treatment, the patients in the stimulation group had significant improvements in responder rate (40.5% for the active group vs. 15.6% for the control group). Additionally, 35 of these 50 patients continued in the long-term study. After 6 and 12 months, the seizure frequency reduction was 27.4% and 34.8%, respectively, in the original stimulation group. The responder rate was 30.6% for all patients combined. There were no serious adverse events.\textsuperscript{95}

Although eTNS is not as effective as VNS based on published studies, it still has several advantages. It is noninvasive and relatively economical. Patients may also benefit from the bilateral stimulation pattern due to the crossed and uncrossed connection of the trigeminal nerve and the rich connection to subcortical structures.\textsuperscript{97}

**rTMS**

The application of TMS dates back to 1985, when Barker et al.\textsuperscript{98} invented the initial TMS device to investigate the influence of stimulation on human motor cortex. rTMS is capable of producing magnetic induction as deep as 2 cm and easily reaching the cortex of the brain. TMS is noninvasive, painless, inexpensive, and has been considered as an efficient tool to modulate cortical excitability and activity.\textsuperscript{99}

The cortical excitability is increased in epilepsy patients.\textsuperscript{100,101} The high cortical excitability and abnormal spreading activity can be reduced by rTMS, and seizures can therefore be prevented.\textsuperscript{102} Current rTMS studies have shown favorable effects in seizure control.\textsuperscript{103–107} There were eight randomized controlled trials that compared rTMS with active or placebo controls (Table 4).\textsuperscript{104,106–111} In a double-blind randomized controlled trial, 21 patients with malformations of cortical development (MCDs) underwent five consecutive sessions of low-frequency rTMS on MCD foci. rTMS significantly decreased seizure frequency in the stimulation group (reduction of 72%) compared to baseline. The effect lasted for >2 months (reduction of 58%). The control group showed no significant changes in seizure frequency. Additionally, there was a significant decrease in epileptiform discharges immediately after (reduction of 31%) and at 4 weeks (reduction of 16%) in the stimulation group only. All patients tolerated rTMS well, without any serious adverse events.\textsuperscript{103} In another controlled study, low-frequency rTMS (0.5 Hz) was delivered to 60 patients with focal epilepsy. In the stimulation group, after 2 weeks of high-intensity (90% resting motor threshold) rTMS treatment, seizure frequency decreased significantly from a baseline of 8.9 ± 11.1 seizures per week to 1.8 ± 3.7. Comparatively, seizure frequency was unchanged in the control group (20% resting motor threshold) at 8.6 ± 10.8 seizures per week at baseline and 8.4 ± 10.1 seizures after 2 weeks. The majority of subjects enrolled were patients with frontal and centroparietal epilepsy, and thus, the targets were easily and precisely reached by stimulation. The patients with mesial temporal epilepsy (n = 2 in the stimulation group) had poor efficacy, which might be due to the deep location of the seizure foci. This study indicated that low-frequency, high-intensity rTMS on seizure foci had an antiepileptic effect on patients with focal seizures, especially neocortical epilepsy.\textsuperscript{104} Six studies failed to show any improvement in seizure frequency, but four of them showed improvement in EEG changes. The reasons for these inconsistent outcomes may include patient selection bias, blinding bias, and different stimulus parameters used. This indicates that localized epileptic foci stimulation with suprathreshold intensity is more likely to lead to better efficacy. Several other reports showed beneficial effects of low-frequency rTMS in patients with status epilepticus.\textsuperscript{112,113}

The available data support that rTMS is effective at reducing epileptiform discharges, but the evidence for seizure reduction is still insufficient. The patient selection, design, and methodology of the double-blind trials, and stimulus parameters used may be responsible for the different results in these studies. These studies indicate that rTMS with more pulses at higher intensity may yield a better outcome. The stimulation target also plays an important role in treatment performance. Neocortical epilepsy with visible lesional MRI in cortical convexity may benefit most from treatment, because the epileptic foci can be reached directly and reliably. Patients with deeper foci, such as mesial temporal epilepsies, are less likely to respond well. These

| Table 3. Summary of clinical data using responsive neurostimulation in epilepsy |
|-----------------------------|-----------------|-----------------|----------------|
| **Reference**               | No. of pts      | Design of study | Seizure type   |
| Bergey (2015)\textsuperscript{94} | 230             | Open-label      | Focal onset    |
| Heck (2014)\textsuperscript{91} | 191             | Double-blind randomized controlled | Focal onset (two seizure foci in 55%) |
| Morrell (2011)\textsuperscript{92} |                 |                 |                |
| **Stimulation parameters** |                  |                  |                |
|                            | NR              | 200 Hz, <12 mA, 160 µs, 5.9 min/day on average |
| **Follow-up, mo**          | 74              | 24              |
| **Results**                | 48–60% median SR | 37.9% in the active group & 17.3% in the sham group |
|                            |                  | 55% RR, 53% median SR |
| **Adverse events**         | Implant site infection (24 pts) | Implant site infection (5 pts) | ICH (4 pts) |

ICH, intracranial hemorrhage; NR, not reported; pts, patients; RR, responder (seizure reduction >50%) rate; SR, seizure reduction.
| Target | Reference | No. of pts | Design of study | Seizure type | Stimulation parameters | Follow-up, mo | Results | Adverse events |
|--------|-----------|------------|----------------|--------------|------------------------|---------------|---------|----------------|
| Epileptogenic foci | Seynave (2016) | 11 | Randomized sham-controlled crossover | Focal onset | 0.5 Hz, 90% RMT, 1,500 pulses, 10 days, figure-of-eight & round coil | 0 | No significant improvement of SR |
| Epileptogenic foci | Sun (2012) | 64 | Single-blind randomized non-placebo-controlled | Focal onset | 0.5 Hz, 3 sessions of 500 pulses w/ 600-s interval, 90% & 20% (control) RMT, 2 weeks, figure-of-eight coil | 2 | Interictal ED significantly decreased |
| Epileptogenic foci | Wang (2008) | 30 | Randomized AED-controlled | Focal onset (temporal lobe epilepsy) | 1 Hz, 90% RMT, 500 pulses, 1 week, figure-of-eight coil | 1 | Interictal ED significantly decreased |
| Vertex | Cantello (2007) | 43 | Double-blind randomized sham-controlled crossover | Focal onset | 0.3 Hz, 500 pulses, 30-s interval, 100% RMT, twice daily for 5 days, round coil | 1.5 | Interictal ED significantly decreased in 33% |
| Epileptogenic foci & vertex (multifocal or nonlocalized) | Joo (2007) | 35 | Double-blind randomized non-placebo-controlled | Focal onset | 0.5 Hz, 1,500 & 3,000 pulses, 100% RMT, 5 days, round coil | 2 | Interictal ED significantly decreased (54.9%) |
| Epileptogenic foci & vertex (multifocal or nonlocalized) | Fregni (2006) | 21 | Double-blind randomized sham-controlled | Focal onset | 1 Hz, 1,200 pulses, 70% RMT, 5 days, figure-of-eight coil | 2 | Interictal ED significantly decreased (16%) at week 4 |
| Vertex | Tergau (2003) | 17 | Randomized crossover | Focal onset (15 pts) & generalized (2 pts) | 0.333, 0.666, & 1 Hz, 1,000 pulses, <100% & 10% (control) RMT, 5 days, round coil | 1 | Significant SR (40%) immediately & 20% at week 2 (0.333 Hz) |
| Epileptogenic foci | Theodore (2002) | 24 | Double-blind randomized placebo-controlled | Focal onset | 1 Hz, 120% RMT, 15 min, twice daily for 1 week, figure-of-eight coil (control: the coil was angled at 90° away from the scalp) | 2 | No significant improvement of SR |

AED, antiepileptic drug; ED, epileptiform discharges; pts, patients; RMT, resting motor threshold; SR, seizure reduction.
patients with visible lesional MRI in cortical convexity are good surgical candidates. Therefore, rTMS may be an option when the epileptic foci involve the eloquent cortex and surgery is not suitable. The potential long-lasting effects of rTMS were considered to be associated with the number of rTMS treatments. It is postulated that the decrease of cortical excitement decreases abnormal excitatory input to the normal surrounding cortex and thus increases inhibitory excitations. However, it is unclear how long this therapeutic effect can last. Large-scale, well-designed clinical trials are necessary to prove the efficacy of rTMS in treating epilepsy, and further investigations of parameters like the stimulation frequency, intensity, train duration, and coil shape should be stressed to confirm and maximize the efficacy in the future.

**tDCS**

Like rTMS, tDCS is another emerging noninvasive stimulation method that could modulate cortical excitability. tDCS changes the resting membrane potential by influencing ion channels and gradients, and inducing changes of cortical excitability. Constant weak currents (1–2 mA) are delivered to seizure foci transcranially via two electrodes. Principally, the cathodal tDCS results in brain hyperpolarization (inhibition) and is proposed to suppress epileptiform discharges and seizures. The first clinical controlled trial enrolled 19 patients with focal refractory epilepsy due to cortical dysplasia. All patients underwent a 20-min session of tDCS (1 mA) targeting the seizure foci. The results showed a 64.3% reduction in epileptiform discharges and a 44.0% reduction in seizure frequency in the stimulation group versus only a 5.8% reduction in epileptiform discharges and an 11.1% reduction in seizure frequency in the control group. San-Juan et al. reviewed three animal studies and six human studies from 1969 to 2013. The animal studies showed that stimulation could decrease epileptiform discharges successfully. Four of six clinical studies showed seizure frequency reduction, and five of six showed reduction in interictal epileptiform discharges as well. All patients tolerated tDCS well, without any serious adverse events. Auvichayapat and colleagues treated 36 children with focal epilepsy using tDCS. The stimulation group (27 patients) showed a significant epileptiform discharges reduction to 45.3% of baseline immediately and 57.6% at 48 h after treatment. However, the clinical seizure frequency showed no significant difference between the stimulation and control groups. In 2016, the same study group treated 22 children with Lennox–Gastaut syndrome with 2-mA cathodal tDCS applied over the left primary motor cortex for 20 min on five consecutive days. The stimulation group (15 patients) showed significant reduction in seizure frequency of 99.8% immediately and 55.96% at 4 weeks after treatment, as well as a reduction in epileptiform discharges of 76.48% immediately and 8.56% at 4 weeks after treatment. Relative to the control group (seven patients), the seizure frequency was significantly decreased immediately (p < 0.001) and at 1 week (p < 0.001), 2 weeks (p < 0.001), 3 weeks (p < 0.001), and 4 weeks (p = 0.002). Some individual seizure types, such as tonic, atonic, and absence seizures, decreased significantly. In another study of mesial temporal lobe epilepsy with hippocampal sclerosis, a total of 12 patients were enrolled and received 2-mA cathodal stimulation applied over the temporal region for 30 min on three consecutive days and also sham stimulation. The seizure frequency decreased from 10.58 per month to 1.67 (p = 0.003). Ten patients (83.33%) had >50% seizure frequency reduction, and six of them became seizure free. After sham stimulation, the seizure frequency did not show any decreases.

Not only did this study show efficacy in seizure control, but tDCS also improved symptoms of depression in patients with epilepsy (Table 5).

Slightly different from rTMS, tDCS is more economical and the device is portable, which will make home treatment possible in the future. tDCS can be used in treating both focal onset and generalized epilepsies in children and adult patients who are not surgical candidates. Especially for those young children who cannot tolerate the pain of magnetic stimulation or who move frequently during treatment, tDCS may be a more acceptable option. The studies of tDCS in the treatment of epilepsy are preliminary and limited, but hold great promise, especially based on several studies in the past year. In all reported studies, the epilepsy types, stimulation paradigms, and efficacies varied. In the future, a better understanding of the intrinsic characteristics of epilepsy networks is needed, and the “hub” needs to be identified for each epilepsy type.

**Summary**

Although neurostimulation is the third-line treatment for epilepsy patients, it provides safe and adjunctive treatment options, especially for patients who are drug-resistant and not suitable for surgery. Past and ongoing clinical investigations prove the efficacy of neurostimulation in drug-resistant epilepsy treatment. The efficacy is mild to moderate and possibly long-lasting. Improvement of seizure frequency and epileptiform discharges are common, but progression to a seizure-free state is rare. Each of the neurostimulation methods have advantages and shortcomings of their own. For invasive stimulation methods such as VNS, DBS, and RNS, the clinical trials are all well-designed and have high levels of evidence. All of them have received approval for the treatment of epilepsy. Future studies should focus on targeting effectively and precisely, minimizing implantation and stimulation-related adverse events, extending battery life, and optimizing cost-effectiveness. The noninvasive stimulations, such as rTMS, tDCS, and eTNS, have no sufficient clinical trials to provide powerful

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*Epilepsia Open, 2(4):371–387, 2017*

doi: 10.1002/epi4.12070
| Target | Reference | No. of pts | Design of study | Seizure type | Stimulation parameters | Follow-up, mo | Results | Adverse events |
|--------|-----------|------------|-----------------|--------------|-----------------------|--------------|---------|----------------|
| Primary motor cortex (M1) | Auvichayapat (2016) | 22 | Double-blind randomized sham-controlled | LGS | 2 mA Sponge electrode 35 cm² 20 min for 5 days | 1 | ED decreased (76.48%) immediately & at week 4 (8.56%) SR (99.84%) immediately & at week 4 (55.96%) | 1-mm superficial skin burn |
| Epileptogenic foci (T3, T4) | Tekturk (2016) | 12 | Randomized crossover | MTLE w/ HS | 2 mA Sponge electrode 35 cm² 30 min for 3 days | 0 | 83.33% RR 84.22% SR | |
| Epileptogenic foci (right temporal) | Zoghi (2016) | 1 | Case report | Temporal lobe epilepsy | 2 mA Sponge electrode 12 cm² 18 min for 2 days | 4 | Significant improvement of SR | |
| Epileptogenic foci (C3, F3) | Auvichayapat (2013) | 36 | Randomized sham-controlled | Focal onset w/ different etiologies | Sponge electrode 35 cm² 20 min | 0 | ED decreased (57.6%) for 48 h 4.8% SR | |
| Epileptogenic foci (C5, C6) | Faria (2012) | 2 | Controlled crossover | CSWS | 1 mA Sponge electrode 35 cm² 3 sessions of 30 min once weekly | 0 | ED decreased (32.1%) | |
| Epileptogenic foci (C3, F2) | San-Juan (2011) | 2 | Case report | Rasmussen encephalitis | 1–2 mA Subdermal needle 60 min in four sessions (on days 0, 7, 30, 60) | 12 | 50% SR (1 pt) & SF (1 pt) Improved alertness & language | |
| Epileptogenic foci | Varga (2011) | 5 | Double-blind sham-controlled crossover | CSWS | 1 mA Sponge electrode 25 cm² 20 min in 2 days | 0 | No significant improvement of spike index | |
| Epileptogenic foci (midpoint between P4 & T4) | Yook (2011) | 1 | Case report | Bilateral perisylvian syndrome (MCD) | 1 mA Sponge electrode 25 cm² 20 min in 10 days, repeat after 2 months | 5 | 87.5% SR | |
| Epileptogenic foci | Fregni (2006) | 19 | Randomized sham-controlled | Focal onset | Sponge electrode 35 cm² 20 min | 1 | ED significantly decreased (64.3%) No significant improvement of SR (44%) | |

CSWS, continuous spikes and waves during slow sleep; ED, epileptiform discharges; HS, hippocampal sclerosis; LGS, Lennox–Gastaut syndrome; MCD, malformations of cortical development; MTLE, mesial temporal lobe epilepsy; pt(s), patient(s); RR, responder (seizure reduction >50%) rate; SF, seizure free; SR, seizure reduction.
evidence of efficacy, although the limited published studies have shown encouraging results. Future studies should focus on stimulating deep brain structures effectively with energy focusing and designing large-scale double-blind randomized controlled trials. Within multiple modalities of neuromodulation, the choice for an optimal neurostimulation treatment should be fully discussed by neurologists and neurosurgeons at a presurgical conference. A combination of different stimulations and multitarget stimulation may be a promising direction in the future.

**Stimulus parameters standard**

The wide range of stimulus parameters poses a difficult challenge in neurostimulation treatment and is responsible for some inconsistent study results. Optimizing stimulus parameters depends on further well-designed large-scale multicenter studies with long-term follow-up. Studies should explore stimulation intensity, frequency, duration, and number of sessions, as well as stimulation targets. Evaluations should include not only the seizure frequency and epileptiform discharges, but also seizure type and severity, and cognitive and psychosocial function. The establishment of a neurostimulation system with standardized stimulus parameters and rigorous guidelines and instructions is imperative, and thus a worldwide collaboration of epilepsy centers is suggested for the future.

**Theoretical research**

The fundamental study on the principles of neurostimulation has developed greatly in the past decades, and has built upon the foundation of neurostimulation in epilepsy treatment discussed here. However, the complete mechanism by which stimulation exerts its therapeutic effect is still unknown. Conversely, the intrinsic characteristics of epilepsy as a “network” also remain unclear. Whether the “hub” exists in specific epilepsy networks requires further elucidation. The abnormal connections in epilepsy networks need to be delineated. Therefore, more theoretical research on the mechanism of epileptogenesis and epilepsy networks is required and may help to determine optimal patient candidates and targets individually.

**Technology advancement**

The development of neurostimulation is based on and driven not only by theoretical research but also by technological advances. The improved understanding of epileptogenesis, as well as patient and clinician demands, has resulted in development of technology. For example, new electrodes need to be designed to minimize the extent of postoperative electrode migration; new stimulation coils need to reach deeper targets in the brain; longer-lasting, rechargeable generators are needed to cut down battery cost; miniaturization of the stimulation systems is needed to decrease adverse effects after implantation; secure wireless remote communication would allow clinicians to modify the stimulation program easily; household devices could facilitate long-term treatment outside hospital, and so on. Progressive improvement and innovation in technology are promising and set to continue. Researchers, engineers, and clinicians will need to communicate with each other and make efforts to offer the best stimulation therapy to patients with drug-resistant epilepsy.

**Disclosure**

The authors declare no conflicts of interest. We confirm that we have read the Journal’s position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

**References**

1. Brodie MJ, Barry SJ, Bamagous GA, et al. Patterns of treatment response in newly diagnosed epilepsy. Neurology 2012;78:1548–1554.

2. Takebayashi S, Hashizume K, Tanaka T, et al. Anti-convulsant effect of electrical stimulation and lesioning of the anterior thalamic nucleus on kainic acid-induced focal limbic seizure in rats. Epilepsy Res 2007;74:163–170.

3. Zabara J. Inhibition of experimental seizures in canines by repetitive vagal stimulation. Epilepsia 1992;33:1005–1012.

4. Rutledge LT, Ranck JB Jr, Duncan JA. Prevention of supersensitivity in partially isolated cerebral cortex. Electroencephalogr Clin Neurophysiol 1967;23:256–262.

5. Cyberonics Inc. Annual Report, 1972. Available at: http://ir.cyberonics.com/annuals.cfm. Accessed June 7, 2015.

6. Ben-Menachem E, Hamberger A, Hedner T, et al. Effects of vagus nerve stimulation on amino acids and other metabolites in the CSF of patients with partial seizures. Epilepsy Res 1995;20:221–227.

7. Martel V, Raedt R, Waebbers T, et al. The effect of vagus nerve stimulation on CSF monoamines and the PTZ seizure threshold in dogs. Brain Stimul 2015;8:1–6.

8. Vagus Nerve Stimulation Study Group. A randomized controlled trial of chronic vagus nerve stimulation for treatment of medically intractable seizures. Neurology 1995;45:224–230.

9. Handforth A, DeGiorgio CM, Schachter SC, et al. Vagus nerve stimulation therapy for partial-onset seizures: a randomized active-control trial. Neurology 1998;51:48–55.

10. Morris GL III, Gloss D, Buchhalter J, et al. Evidence-based guideline update: vagus nerve stimulation for the treatment of epilepsy: report of the Guideline Development Subcommittee of the American Academy of Neurology. Neurology 2013;81:1453–1459.

11. Schulze-Bonhage A. Brain stimulation as a neuromodulatory epilepsy therapy. Seizure 2016;44:169–175.

12. Serdaroglu A, Arhan E, Kurt G, et al. Long term effect of vagus nerve stimulation in pediatric intractable epilepsy: an extended follow-up. Childs Nerv Syst 2016;32:641–646.

13. Englot DJ, Rolston JD, Wright CW, et al. Rates and predictors of seizure freedom with vagus nerve stimulation for intractable epilepsy. Neurosurgery 2016;79:345–353.

14. Callaghan BC, Anand K, Hesdorffer D, et al. Likelihood of seizure remission in an adult population with refractory epilepsy. Ann Neurol 2007;62:382–389.

15. Choi H, Heiman G, Pandis D, et al. Seizure remission and relapse in adults with intractable epilepsy: a cohort study. Epilepsia 2008;49:1440–1445.

16. Panebianco M, Rigby A, Weston J, et al. Vagus nerve stimulation for partial seizures. Cochrane Database Syst Rev 2015;(4):CD002896.

17. Panebianco M, Zavanone C, Dupont S, et al. Vagus nerve stimulation therapy in partial epilepsy: a review. Acta Neurol Belg 2016;116:241–248.

18. Revesz D, Rydenhag B, Ben-Menachem E. Complications and safety of vagus nerve stimulation: 25 years of experience at a single center. J Neurosurg Pediatr 2016;18:97–104.
68. Bondallaz P, Boex C, Rossetti AO, et al. Electrode location and clinical outcome in hippocampal electrical stimulation for mesial temporal lobe epilepsy. *Seizure* 2013;22:390–395.

69. Min B, Guoming L, Jian Z. Treatment of mesial temporal lobe epilepsy with amygdalotomypallidotomy: a case series and review of the literature. *Exp Ther Med* 2013;5:1264–1268.

70. Cukiert A, Cukiert CM, Burattini JA, et al. Seizure outcome after hippocampal deep brain stimulation in a prospective cohort of patients with refractory temporal lobe epilepsy. *Seizure* 2014;23:6–9.

71. Lim SN, Lee CY, Lee ST, et al. Low and high frequency hippocampal stimulation for drug-resistant mesial temporal lobe epilepsy. *Neuromodulation* 2016;19:365–372.

72. Jin H, Li W, Dong C, et al. Hippocampal deep brain stimulation in nonlesional refractory mesial temporal lobe epilepsy. *Seizure* 2016;37:1–7.

73. Boon P, Vonck K, De Herdt V, et al. Deep brain stimulation in patients with refractory temporal lobe epilepsy. *Epilepsia* 2007;48:1551–1560.

74. Andrade DM, Hamani C, Lozano AM, et al. Dravet syndrome and deep brain stimulation: seizure control after 10 years of treatment. *Epilepsia* 2010;51:1314–1316.

75. Boëx C, Vuillemez S, Spinelli L, et al. High and low frequency electrical stimulation in non-lesional temporal lobe epilepsy. *Seizure* 2017;56:64–69.

76. Parent M, Parent A. Single-axon tracing and three-dimensional reconstruction of centre median-parafascicular thalamic neurons in primates. *J Comp Neurol* 2005;481:127–144.

77. Velasco M, Velasco F, Velasco AL, et al. Electrocortical and behavioral responses produced by acute electrical stimulation of the human centromedial thalamic nucleus. *Electroencephalogr Clin Neurophysiol* 2011;122:461–471.

78. Zamsteg D, Lozano AM, Wennberg RA. Rhythmic cortical EEG synchrony with low frequency stimulation of the anterior and medial thalamus for epilepsy. *Clin Neurophysiol* 2006;117:2272–2278.

79. Cukiert A, Cukiert CM, Argentoni-Baldocchi M, et al. Intraoperative neurophysiological responses in epileptic patients submitted to hippocampal and thalamic deep brain stimulation. *Seizure* 2011;20:748–753.

80. Kim SH, Son BC, Lim SC, et al. EEG driving response during low-frequency stimulation of anterior thalamic nucleus: is it a good predictor of the correct location of DBS electrode? *Clin Neurophysiol* 2014;125:1065–1066.

81. Kim S, Son B, Lim SC, et al. Reply to “recruitment responses have no localizing value.” *Clin Neurophysiol* 2015;126:644–645.

82. Son BC, Shon YM, Kim SH, et al. Relationship between postoperative EEG driving response and lead location in deep brain stimulation of the anterior nucleus of the thalamus for refractory epilepsy. *Stereotact Funct Neurosurg* 2016;94:336–341.

83. Baizabal Carvallo JF, Mostile G, Almaguer M, et al. Deep brain stimulation hardware complications in patients with movement disorders: risk factors and clinical correlations. *Stereotact Funct Neurosurg* 2012;90:300–306.

84. Boviatisis EJ, Stavrinou LC, Themistocleous M, et al. Surgical and hardware complications of deep brain stimulation. A seven-year experience and review of the literature. *Acta Neurochir* 2010;152:2053–2062.

85. Doshi PK. Long-term surgical and hardware-related complications of deep brain stimulation. *Stereotact Funct Neurosurg* 2011;89:89–95.

86. Chan DT, Zhu XL, Yeung JH, et al. Complications of deep brain stimulation: a collective review. *Asian J Surg* 2009;32:258–263.

87. Parriottokaporn T, Thomas DG, Schneider A, et al. Microtextured surfaces for deep-brain stimulation electrodes: a biologically inspired design to reduce lead migration. *World Neurosurg* 2012;77:569–576.

88. Pietzsch JB, Garner AM, Marks WJ Jr. Cost-effectiveness of deep brain stimulation for advanced Parkinson’s disease in the United States. *Neuromodulation* 2016;19:689–697.

89. Zhu XL, Chan DT, Lau CK, et al. Cost-effectiveness of subthalamic nucleus deep brain stimulation for the treatment of advanced Parkinson’s disease in Hong Kong: a prospective study. *World Neurosurg* 2014;82:987–993.

90. Thomas GP, Jobst BC. Critical review of the responsive neurostimulator system for epilepsy. *Med Devices (Auckl)* 2015;8:405–411.

91. Heck CN, King-Stephens D, Massey AD, et al. Two-year seizure reduction in adults with medically intractable partial onset epilepsy treated with responsive neurostimulation: final results of the RNS System Pivotal trial. *Epilepsia* 2014;55:432–441.

92. Morrell MJ. Responsive cortical stimulation for the treatment of medically intractable partial epilepsy. *Neurology* 2011;77:1295–1304.

93. Meador KJ, Kapur R, Loring DW, et al. Quality of life and mood in patients with medicially intractable epilepsy treated with targeted responsive neurostimulation. *Epilepsy Behav* 2015;45:242–247.

94. Bergey GK, Morrell MJ, Mizzahl EM, et al. Long-term treatment with responsive brain stimulation in adults with refractory partial seizures. *Neurology* 2015;84:810–817.

95. Soss J, Heck C, Murray D, et al. A prospective long-term study of external trigeminal nerve stimulation for drug-resistant epilepsy. *Epilepsy Behav* 2015;42:44–47.

96. DeGiorgio CM, Soss J, Cook IA, et al. Randomized controlled trial of trigeminal nerve stimulation for drug-resistant epilepsy. *Neurology* 2013;80:786–791.

97. Faught E, Tatum W. Trigeminal stimulation: a superhighway to the brain? *Neurology* 2013;80:780–781.

98. Barker AT, Jalinous R, Freeston IL. Non-invasive magnetic stimulation of human motor cortex. *Lancet* 1985;1:1106–1107.

99. Pascual-Leone A, Tormos JM, Keenan J, et al. Study and modulation of human cortical excitability with transcranial magnetic stimulation. *J Clin Neurophysiol* 1998;15:333–343.

100. Badawy RA, Vodrig SJ, Lai A, et al. Patterns of cortical hyperexcitability in adolescent/adult-onset generalized epilepsies. *Epilepsia* 2013;54:871–878.

101. Badawy RA, Vodrig SJ, Lai A, et al. Capturing the epileptic trait: cortical excitability measures in patients and their unaffected siblings. *Brain* 2013;136:1177–1191.

102. Noohi S, Amirsalar S. History, studies and specific uses of repetitive transcranial magnetic stimulation (rTMS) in treating epilepsy. *Iran J Child Neurol* 2016;10:1–8.

103. Fregni F, Otachi PT, Do Valle A, et al. A randomized clinical trial of repetitive transcranial magnetic stimulation in patients with refractory epilepsy. *Ann Neurol* 2006;60:447–455.

104. Sun W, Mao W, Meng X, et al. Low-frequency repetitive transcranial magnetic stimulation for the treatment of refractory partial epilepsy: a controlled clinical study. *Epilepsia* 2012;53:1782–1789.

105. Santiago-Rodriguez E, Cardenas-Morales L, Harmony T, et al. Repetitive transcranial magnetic stimulation decreases the number of seizures in patients with focal neocortical epilepsy. *Seizure* 2008;17:677–683.

106. Theodore WH, Hunter K, Chen R, et al. Transcranial magnetic stimulation for the treatment of seizures: a controlled study. *Neurology* 2002;59:560–562.

107. Cantello R, Rossi S, Varrazi C, et al. Slow repetitive TMS for drug-resistant epilepsy: clinical and EEG findings of a placebo-controlled trial. *Epilepsia* 2007;48:366–374.

108. Joo EY, Han SJ, Chung SH, et al. Antiepileptic effects of low-frequency repetitive transcranial magnetic stimulation by different stimulation durations and locations. *Clin Neurophysiol* 2007;118:702–708.

109. Tergau F, Neumann D, Rosenow F, et al. Can epilepsies be improved by repetitive transcranial magnetic stimulation?—interim analysis of a controlled study. *Sappi Clin Neurophysiol* 2003;56:400–405.

110. Wang X, Yang D, Wang S, et al. Effects of low-frequency repetitive transcranial magnetic stimulation on electroencephalogram and seizure frequency in 15 patients with temporal lobe epilepsy following dipole source localization. *Neural Regen Res* 2008;3:1257–1260.

111. Seynave L, Devroye A, Dupont P, et al. Randomized crossover sham-controlled clinical trial of targeted low-frequency transcranial magnetic stimulation comparing a figure-8 and a round coil to treat refractory neocortical epilepsy. *Epilepsia* 2016;57:141–150.

112. Liu A, Pang T, Herman S, et al. Transcranial magnetic stimulation for refractory focal status epilepticus in the intensive care unit. *Seizure* 2013;22:893–896.

113. Thordstein M, Constantinescu R. Possibly lifesaving, noninvasive, EEG-guided neuromodulation in anesthesia-refractory partial status epilepticus. *Epilepsy Behav* 2011;22:468–472.

114. Fregni F, Pascual-Leone A. Technology insight: noninvasive brain stimulation in neurology-panoramas on the therapeutic potential of rTMS and DCS. *Nat Clin Pract Neurol* 2007;3:383–393.
115. Nitsche MA, Cohen LG, Wassermann EM, et al. Transcranial direct current stimulation: state of the art 2008. *Brain Stimul* 2008;1:206–223.

116. Nitsche MA, Paulus W. Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. *J Physiol* 2000;527(pt 3):633–639.

117. Fregni F, Thome-Souza S, Nitsche MA, et al. A controlled clinical trial of cathodal DC polarization in patients with refractory epilepsy. *Epilepsia* 2006;47:335–342.

118. San-Juan D, Morales-Quezada L, Orozco Garduno AJ, et al. Transcranial direct current stimulation in epilepsy. *Brain Stimul* 2015;8:455–464.

119. Auvichayapat N, Rothenberg A, Gersner R, et al. Transcranial direct current stimulation for treatment of refractory childhood focal epilepsy. *Brain Stimul* 2013;6:696–700.

120. Auvichayapat N, Sinsupan K, Tunkamnerdthai O, et al. Transcranial direct current stimulation for treatment of childhood pharmacoresistant Lennox-Gastaut syndrome: a pilot study. *Front Neurol* 2016;7:66.

121. Tekturk P, Erdogan ET, Kurt A, et al. The effect of transcranial direct current stimulation on seizure frequency of patients with mesial temporal lobe epilepsy with hippocampal sclerosis. *Clin Neurol Neurosurg* 2016;149:27–32.

122. Liu A, Bryant A, Jefferson A, et al. Exploring the efficacy of a 5-day course of transcranial direct current stimulation (TDCS) on depression and memory function in patients with well-controlled temporal lobe epilepsy. *Epilepsy Behav* 2016;55:11–20.

123. Zoghi M, O’Brien TJ, Kwan P, et al. The effects of cathodal transcranial direct current stimulation in a patient with drug-resistant temporal lobe epilepsy (Case Study). *Brain Stimul* 2016;9:790–792.

124. Faria P, Fregni F, Sebastiao F, et al. Feasibility of focal transcranial DC polarization with simultaneous EEG recording: preliminary assessment in healthy subjects and human epilepsy. *Epilepsy Behav* 2012;25:417–425.

125. San-Juan D, Calcaneo Jde D, Gonzalez-Aragon MF, et al. Transcranial direct current stimulation in adolescent and adult Rasmussen’s encephalitis. *Epilepsy Behav* 2011;20:126–131.

126. Varga ET, Terney D, Atkins MD, et al. Transcranial direct current stimulation in refractory continuous spikes and waves during slow sleep: a controlled study. *Epilepsy Res* 2011;97:142–145.

127. Yook SW, Park SH, Seo JH, et al. Suppression of seizure by cathodal transcranial direct current stimulation in an epileptic patient—a case report. *Ann Rehabil Med* 2011;35:579–582.