

Neurostimulation as a promising epilepsy therapy

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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.



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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.¹ 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

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KEY POINTS

- The fast development of neurostimulation has led to the advent of an “era of neurostimulation” in antiepileptic treatment
- Benefits of various neurostimulation modalities are compared based on recent evidence
- Stimulus parameter standardization, theoretic research, and technology advancement may be future directions for the development of neurostimulation

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.^{2–5} 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.⁴ A report in 1972 showed that over 85,000 epilepsy patients had VNS devices implanted.⁵ In

Table 1. Devices of neurostimulation

Neurostimulation techniques	Devices
VNS	Implantable VNS therapy system (the NeuroCybernetic Prosthesis System) NEMOS transcutaneous VNS AspireSR generator
DBS	Medtronic DBS leads (Medtronic, Minneapolis, MN, U.S.A.) Modified Resume 4-button electrodes (Medtronic) Electrodes & transmitters (Avery Laboratories, Farmingdale, NY, U.S.A.)
RNS	The RNS System (NeuroPace)
rTMS	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.)
tDCS	Nicolet Endeavor CR (VIASYS Healthcare, U.S.A.) & disposable stainless-steel subdermal needle (Cardinal Health, U.S.A.) Stimulator (Schneider Electronic, Gleichen, 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 Intellect Advanced Combo)

DBS, deep brain stimulation; RNS, responsive neurostimulation; rTMS, repetitive transcranial magnetic stimulation; tDCS, transcranial direct current stimulation; VNS, vagus nerve stimulation.

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.^{6,7} Early in the 1990s, two double-blind randomized controlled trials showed a seizure frequency reduction of 24.5% in the high-stimulation group versus only 6.1% in the low-stimulation group at the 14-week time point⁸ and a seizure frequency reduction of 28% in the high-stimulation group versus 15% in the low-stimulation group at the 3-month time point.⁹ A review including studies from 1999 to 2012 showed VNS achieved >50% seizure frequency reduction in 55% of 470 children with focal or generalized epilepsy (13 class III studies), as well as >50% seizure frequency reduction in 55% of 113 patients with Lennox–Gastaut syndrome (4 class III studies). In addition, VNS may have increased efficacy over time and improve mood in adults with epilepsy.¹⁰ The long-term effects of VNS suggest that it may not only work through immediate stimulation effects but also through the remodulation of epilepsy networks to a less

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 decreased 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,^{24–38} 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.²⁰ 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

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) ²⁷	1	Open-label	Focal onset	NR	12	>60% SR	Increased aggression
ANT	Krishna (2016) ²⁸	16	Open-label	Generalized & focal onset	100–185 Hz, 2.4–7 V, 90 μ s, 1 min on/5 min off	14–153	11.5% median SR 69% RR insertional effect observed	
ANT	Lehtimäki (2016) ³¹	15	Open-label	Focal onset	140 Hz, 5 V, 90 μ s, 1 min on/5 min off	25.2 (9–52)	67% SR	Psychiatric (4 pts)
ANT	Salanova (SANTE; 2015) ²⁹	83	Double-blind randomized controlled	Focal onset	145 Hz, 5 V, 90 μ s, 1 min on/5 min off	61	69% median SR TLE: 76% SR FLE: 59% SR Other: 68% SR	Implant site pain (20.9%) Implant site infection (12.7%) Paresthesias (22.7%) Memory impairment (6.4%) Discomfort (9.1%) SUDEP not related to DBS (1 pt)
ANT	Piacentino (2015) ³⁰	6	Open-label	Focal onset	130–140 Hz, 4 V, 90 μ s	12–48	33–80% SR	
ANT	Oh (2012) ³²	9	Open-label	Focal onset	100–185 Hz, 1.5–3.1 V, 90–150 μ s, continuous	34.6 (22–60)	No improvement (1 pt) 57.9% median SR	
ANT	Lee (2012) ²⁵	15	Open-label	Generalized & focal onset	100–185 Hz, 1.5–3.1 V, 90–150 μ s, continuous	39 (24–67)	70.5% median SR	Wound infection (1 pt)
ANT	Andrade (2010) ⁷⁴	2	Open-label	Dravet syndrome	NR	120	67–98% SR	Replacement for incorrect positioning (8.2%)
ANT	Fisher (SANTE; 2010) ²⁶	110	Double-blind randomized controlled	Focal onset	145 Hz, 5 V, 90 μ s, 1 min on/5 min off	24	56% median SR Insertional effect observed	Implant site pain (10.9%) Implant site infection (12.7%) Asymptomatic ICH (4.5%) Paresthesias (18.2%)
ANT	Osorio (2007) ³³	4	Open-label	MTLE	175 Hz, 4.1 V, 90 μ s	36	53.4–92.8% SR	Small ICH (1 pt)
ANT	Lim (2007, 2008) ^{34,35}	4	Open-label	Generalized & focal onset	90–100 Hz, 4–5 V, 60–90 μ s	24	35–76% SR Insertional effect observed	Extension erosion over scalp (1 pt) Lethargy (1 pt)
ANT	Andrade (2006) ²⁴	6	Open-label	Generalized & focal onset	100–185 Hz, 1–10 V, 90–120 μ s, 1 min on/4 or 5 min off	60	100% RR	
ANT	Lee (2006) ³⁶	3	Open-label	Focal onset	130 Hz, 90 μ s, 1 min on/5 min off, alternating left–right	15–450	75.4% median SR	
ANT	Kerrigan (2004) ³⁷	5	Open-label	Focal onset	100 Hz, 1–10 V, 90 μ s, 1 min on/10 min off, alternating left–right	20.4 (6–36)	80% RR of injurious seizures No improvement (1 pt)	Replacement for incorrect positioning (1 pt)
ANT	Hodaie (2002) ³⁸	5	Open-label	Generalized & focal onset	100 Hz, 10 V, 90 μ s, 1 min on/5 min off, alternating left–right	14.9 (10.6–20.7)	24–89% SR	Skin erosion (1 pt)

Continued

Table 2. Continued.

Target	Reference	No. of pts	Design of study	Seizure type	Stimulation parameters	Follow-up, mo	Results	Adverse events
CM	Valentín (2017) ²⁷	2	Open-label	Generalized	NR	18–48	>60% SR (1 pt) No improvement (1 pt) 68% median SR	
CM	Son (2016) ⁴¹	14	Open-label	LGS & multilobar	120–130 Hz, 0–2.6 V, 90–150 μ s	18	100% RR (LGS) 70% RR (multilobar)	Implant site infection (1 pt)
CM	Valentín (2013) ⁴⁴	11	Single-blind controlled	Generalized & focal onset	60–130 Hz, <5 V, 90 μ s, bilateral	24 (12–66)	83% RR (generalized) 20% RR (focal onset)	
CM	Cukiert (2009) ⁴³	4	Open-label	Generalized	130 Hz, 2 V, 300 μ s, bilateral	18 (12–24)	65–98% SR Increased attention	
CM	Velasco (2006) ³⁹	13	Open-label	LGS	130 Hz, 400–600 μ A, 450 μ s	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 μ s, 1 min on/4 or 5 min off	24–84	No improvement	Intermittent nystagmus (1 pt) Possible auditory hallucinations & anorexia (1 pt)
CM	Velasco (2000) ⁴⁰	13	Double-blind	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 (sGTCS)	
CM	Fisher (1992) ⁴²	7	Double-blind crossover	Generalized	65 Hz, 0.5–10 V, 90 μ s, 1 min on/4 min off, bilateral 2 h/day	12–22	30% median SR (GTCS) 50% RR (stimulation) 24 h/day	Asymptomatic ICH (1 pt)
STN	Capecchi (2012) ⁴⁹	2	Open-label	Generalized & focal onset	130 Hz, 0–5 V, 90 μ s, 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 μ s, bilateral	12	50% SR	
STN	Lee (2006) ³⁶	3	Open-label	Focal onset	5–10 Hz, 3–7 V, 90 μ s	1–30	49.1% median SR	Wound infection (1 pt)
STN	Handforth (2006) ⁴⁵	2	Open-label	Focal onset	130–185 Hz, <3.5 V, 60–90 μ s, bilateral	26–32	33–50% SR	
STN	Shon (2005) ⁴⁷	2	Open-label	Focal onset	130 Hz, 60–90 μ s	6–18	86.7–88.6% SR	
STN	Chabardès (2002) ⁴⁶	5	Open-label	Focal onset, Dravet syndrome, & ADFLE	130 Hz, 1.5–5.2 V, 90 μ s, continuous	10–30	67–80.7% SR (3 pts) 41.5% in Dravet syndrome	Infection of generator (1 pt) Postimplantation subdural hematoma (1 pt)
Cerebellum	Velasco (2005) ⁵¹	5	Double-blind randomized controlled	Generalized	2 μ C/cm ² /phase, 10–20 Hz, 3.8 mA, 2.28 V, 450 μ s	10–48	No improvement in autosomal dominant frontal lobe epilepsy 76% median SR (GTCS) 57% median SR (tonic)	Infection (1 pt) Lead displacement (3 pts)

Continued

Table 2. Continued.

Target	Reference	No. of pts	Design of study	Seizure type	Stimulation parameters	Follow-up, mo	Results	Adverse events
Cerebellum	Davis (1992) ⁵⁸	27	Open-label	Heterogenous	0.8–2.5 $\mu\text{C}/\text{cm}^2$ /phase, 150–180 Hz, 0.5–1.4 mA, 2.28 V, 500 μs 10 Hz, 1–7 mA	24–204	44% SF 41% reduction 15% no improvement No significant improvement	Wound infection (2 pts)
Cerebellum	Wright (1984) ⁵⁷	12	Double-blind	Generalized & focal onset	10 Hz, 2.25–8 V, alternating left–right	6	27–100% SR (3 pts)	Mechanical failed (1 pt) Wound infection (2 pts)
Cerebellum	Levy (1979) ⁵⁴	6	Open-label	Generalized & focal onset	10–14 V, 10 & 200 Hz, alternating left–right	7–20	No improvement in 3 pts	Skin erosion (1 pt) Headache (all pts)
Cerebellum	Van Buren (1978) ⁵³	5	Double-blind	Generalized & focal onset	10 & 200 Hz	24–29	No improvement	CSF leakage (3 pts)
Cerebellum	Cooper (1978) ⁵⁶	29	Open-label	Focal onset	10 & 200 Hz	25	62% pts with clinically significant improvement	
Cerebellum	Sramka (1976) ⁵²	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) ⁵⁵	15	Open-label	Generalized & focal onset	10 Hz, 10 V	11–38	73% pts with clinical improvement	
Hippocampus	Lim (2016) ⁷¹	5	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	3	Open-label	MTLE	130–170 Hz, <3.5 V, 450 μs , unilateral, bilateral	34.7 (26–43)	93% median SR	
Hippocampus	Cukiert (2014) ⁷⁰	9	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) ⁶⁷	11	Open-label	MTLE	130 Hz, 1–3.1 V, 450 μs , unilateral, bilateral	96 (67–120)	70% median SR 80% RR	
Hippocampus	Bondallaz (2013) ⁶⁸	8	Open-label	MTLE	130 Hz, 0.5–2 V, 450 μs , unilateral	18	67% median SR 75% RR	
Hippocampus	Min (2013) ⁶⁹	2	Open-label	MTLE	130 Hz, 2.6–3.6 V, 450 μs , 60 s on/180 s off	18–36	65–90% SR	
Hippocampus	Tyrand (2012) ⁶⁶	12	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) ⁶⁵	8	Open-label	MTLE	130 Hz, 0.5–2 V, 450 μs , unilateral, continuous	43.5 (12–74)	75% RR	Lead displacement (1 pt) Reversible memory impairment (2 pts)
Hippocampus	McLachlan (2010) ⁶⁴	2	Double-blind randomized controlled crossover	Temporal epilepsy	185 Hz, 90 μs , bilateral	3	33% median SR	

Continued

Table 2. Continued.

Target	Reference	No. of pts	Design of study	Seizure type	Stimulation parameters	Follow-up, mo	Results	Adverse events
Hippocampus	Boon (2007) ⁷³	10	Open-label	Temporal lobe onset	130–200 Hz, 2–3 V, 450 μ s, unilateral, bilateral	31 (15–52)	70% RR	Asymptomatic ICH (1 pt)
Hippocampus	Velasco (2007) ⁶³	9	Double-blind	MTLE	130 Hz, 300 μ A, 450 μ s, 1 min on/4 min off, bilateral 20%, unilateral 80%	18	55% RR	Skin erosion & implant site infection (3 pts)
Hippocampus	Tellez-Zenteno (2006) ⁶²	4	Double-blind randomized controlled multiple crossover	MTLE	190 Hz, 90 μ s	6	15% SR	
Hippocampus	Vonck (2005) ⁶¹	7	Open-label	Temporal onset	Unilateral	14 (5.5–21)	57% RR	
Hippocampus	Vonck (2002) ⁶⁰	3	Open-label	Temporal onset	130–200 Hz, 1.0 V, 450 μ s, unilateral	5 (3–6)	100% RR 77% median SR	
Hippocampus	Velasco (2000) ⁵⁹	10	Open-label	Bilateral temporal onset	130 Hz, 200–400 μ A, 450 μ s, 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; SUDEF, sudden unexpected death in epilepsy; MTLE, mesial temporal lobe epilepsy; ICH, intracranial hemorrhage; CM, centromedian thalamic; LGS, Lennox-Gaust syndrome; sGTCS, secondary generalized tonic-clonic seizures; GTCS, generalized tonic-clonic seizures; STN, subthalamic nucleus; PME, progressive myoclonic epilepsy; ADLE, 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%.^{25,27,31–33,36,74} 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.³¹ Krishna et al.²⁸ noted that a more efficient stimulation site was an anteroventral subdivision of ANT because of its close proximity with the mammillothalamic tract. Not only did seizure frequency decrease, but also ANT DBS showed potential improvements in verbal recall and oral information processing, which probably resulted from the bilateral activation of the frontolimbic circuit.³²

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,^{53,57} whereas the third showed seizure reduction up to 57–76%.⁵¹ 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,^{62–64} whereas other open-label studies showed 45–93% seizure reduction and 57–100% responder rate. Velasco et al.⁶³ 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.⁶⁶ 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.⁶⁷ noted that bilateral rather than unilateral stimulation might have superior efficacy in unilateral mesial temporal epilepsy. Lim et al.⁷¹ 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.⁷⁵ 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 study⁶⁸ 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 cortex⁷⁶ and role in gatekeeping and rhythm-generating activities.²⁶ 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.^{36,45–49}

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.^{37,38,44,77–79} However, the localization value of DR as a predictor of correct electrode placement within the thalamus is still controversial.^{78,80,81} 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.⁸² Zumsteg et al.⁷⁸ 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 movement 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 differences 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 warranted 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 seizures 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 neurologists. 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 system acquired FDA approval for the treatment of adult (18 years or older) focal onset refractory epilepsy (refractory 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 continuously 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 individually. When these tools detect abnormal EEG activity, a biphasic electric stimulus is given between two of the electrodes 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 randomized controlled trial, 191 patients with refractory focal seizures with baseline seizure frequency of ≥ 3 disabling seizures 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 hemorrhage occurred in four subjects (2.1%). The patients tolerated RNS well, with no deterioration in mood or neuropsychological function.^{91–93} In an ongoing 7-year multicenter prospective open-label study, the median seizure 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 epilepsy 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 normal brain function, thus resulting in fewer adverse events. For optimal treatment effects, a precise localization of seizure 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 of 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 noninvasive 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

Table 3. Summary of clinical data using responsive neurostimulation in epilepsy

Reference	No. of pts	Design of study	Seizure type	Stimulation parameters	Follow-up, mo	Results	Adverse events
Bergey (2015) ⁹⁴	230	Open-label	Focal onset	NR	74	48–60% median SR	Implant site infection (24 pts)
Heck (2014) ⁹¹ Morrell (2011) ⁹²	191	Double-blind randomized controlled	Focal onset (two seizure foci in 55%)	200 Hz, <12 mA, 160 μ s, 5.9 min/day on average	24	37.9% in the active group & 17.3% in the sham group 55% RR 53% median SR	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.

the supraorbital nerves. In a randomized controlled trial, DeGiorgio et al.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.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.⁹⁷

rTMS

The application of TMS dates back to 1985, when Barker et al.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.⁹⁹ The cortical excitability is increased in epilepsy patients.^{100,101} The high cortical excitability and abnormal spreading activity can be reduced by rTMS, and seizures can therefore be prevented.¹⁰² Current rTMS studies have shown favorable effects in seizure control.^{103–107} There were eight randomized controlled trials that compared rTMS with active or placebo controls (Table 4).^{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.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.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.^{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 4. Summary of clinical data using repetitive transcranial magnetic stimulation in epilepsy

Target	Reference	No. of pts	Design of study	Seizure type	Stimulation parameters	Follow-up, mo	Results	Adverse events
Epileptogenic foci	Seynaeve (2016) ¹¹¹	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) ¹⁰⁴	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) ¹¹⁰	30	Randomized AED-controlled	Focal onset (temporal lobe epilepsy)	1 Hz, 90% RMT, 500 pulses, 1 week, figure-of-eight coil	1	Significant SR Interictal ED significantly decreased	
Vertex	Cantello (2007) ¹⁰⁷	43	Double-blind randomized sham-controlled crossover	Focal onset (41 pts) & generalized (2 pts)	0.3 Hz, 500 pulses, 30-s interval, 100% RMT, twice daily for 5 days, round coil	1.5	No significant improvement of SR Interictal ED significantly decreased in 33%	
Epileptogenic foci & vertex (multifocal or nonlocalized)	Joo (2007) ¹⁰⁸	35	Double-blind randomized non-placebo-controlled	Focal onset	0.5 Hz, 1,500 & 3,000 pulses, 100% RMT, 5 days, round coil	2	No significant improvement of SR Interictal ED significantly decreased (54.9%)	
Epileptogenic foci & vertex (multifocal or nonlocalized)	Fregni (2006) ¹⁰³	21	Double-blind randomized sham-controlled	Focal onset	1 Hz, 1,200 pulses, 70% RMT, 5 days, figure-of-eight coil	2	No significant improvement of SR Interictal ED significantly decreased (16%) at week 4	
Vertex	Tergau (2003) ¹⁰⁹	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 (58%) at month 2	
Epileptogenic foci	Theodore (2002) ¹⁰⁶	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	Significant SR (40%) immediately & 20% at week 2 (0.333 Hz)	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 drive back to the dysplastic cells.¹⁰³ 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.^{114,115} 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.¹¹⁶ 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.¹¹⁷ 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.¹¹⁸ Auvichayapat and colleagues treated 36 children with focal epilepsy using tDCS. The stimulation group (27 patients) showed a significant epileptic discharge 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.¹¹⁹ 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 99.84% 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.¹²⁰ 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.¹²¹ Not only did this study show efficacy in seizure control, but tDCS also improved symptoms of depression in patients with epilepsy (Table 5).¹²²

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

Table 5. Summary of clinical data using transcranial direct current stimulation in epilepsy

Target	Reference	No. of pts	Design of study	Seizure type	Stimulation parameters	Follow-up,		Results	Adverse events
						mo	no		
Primary motor cortex (M1)	Auvichayapat (2016) ¹²⁰	22	Double-blind randomized sham-controlled	LGS	2 mA Sponge electrode 35 cm ² 20 min for 5 days	1	1	ED decreased (76.48%) immediately & at week 4 (8.56%) SR (99.84%) immediately & at week 4 (55.96%) 83.33% RR 84.22% SR	1-mm superficial skin burn
Epileptogenic foci (T3, T4)	Tekturk (2016) ¹²¹	12	Randomized crossover	MTLE w/ HS	2 mA Sponge electrode 35 cm ² 30 min for 3 days	0	0	83.33% RR 84.22% SR	
Epileptogenic foci (right temporal)	Zoghi (2016) ¹²³	1	Case report	Temporal lobe epilepsy	2 mA Sponge electrode 12 cm ² 18 min for 2 days	4	4	Significant improvement of SR	
Epileptogenic foci (C3, F3)	Auvichayapat (2013) ¹¹⁹	36	Randomized sham-controlled	Focal onset w/ different etiologies	1 mA Sponge electrode 35 cm ² 20 min	0	0	ED decreased (57.6%) for 48 h 4.8% SR	Transient erythematous (1 pt)
Epileptogenic foci (C5, C6)	Faria (2012) ¹²⁴	2	Controlled crossover	CSWS	1 mA Sponge electrode 35 cm ² 3 sessions of 30 min once weekly	0	0	ED decreased (32.1%)	
Epileptogenic foci (C3, F2)	San-Juan (2011) ¹²⁵	2	Case report	Rasmussen encephalitis	1–2 mA Subdermal needle 60 min in four sessions (on days 0, 7, 30, 60)	12	12	50% SR (1 pt) & SF (1 pt) Improved alertness & language	
Epileptogenic foci	Varga (2011) ¹²⁶	5	Double-blind sham-controlled crossover	CSWS	1 mA Sponge electrode 25 cm ² 20 min in 2 days	0	0	No significant improvement of spike index 87.5% SR	
Epileptogenic foci (midpoint between P4 & T4)	Yook (2011) ¹²⁷	1	Case report	Bilateral perisylvian syndrome (MCD)	1 mA Sponge electrode 25 cm ² 20 min in 10 days, repeat after 2 months	5	5		
Epileptogenic foci	Fregni (2006) ¹¹⁷	19	Randomized sham-controlled	Focal onset	1 mA Sponge electrode 35 cm ² 20 min	1	1	ED significantly decreased (64.3%) No significant improvement of SR (44%)	Itching

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.

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