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Review

Neurostimulation in the treatment of refractory and super-refractory status epilepticus

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ABSTRACT

Status epilepticus (SE) is a life-threatening condition with a mortality of up to 60% in the advanced and comatose forms of SE. In one out of five adults, first and second line fails to control epileptic activity, leading to refractory status epilepticus (RSE) and in around 3% to super-refractory status epilepticus (SRSE), where SE continues despite anesthetic treatment for 24 h or more. In this rare but devastating condition, innovative and safe treatments are needed. In a recent review on the use of vagal nerve stimulation in RSE and SRSE, a 74% response rate for abrogation of SE was reported. Here, we review the currently available evidence supporting the use of neurostimulation, including vagal nerve stimulation, direct cortical stimulation, transcranial magnetic stimulation, electroconvulsive therapy, and deep brain stimulation in RSE and SRSE.

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1. Introduction

Status epilepticus (SE) represents a neurological and medical emergency associated with high mortality and morbidity. More specifically, generalized (tonic–clonic) convulsive SE and comatose nonconvulsive SE (NCSE) can be life-threatening, with a mortality up to 60% [1]. The pharmacological treatment of convulsive SE is based on a stepwise approach, with benzodiazepines being the first-line treatment. However, in approximately 30–40% of cases, SE cannot be adequately controlled by benzodiazepines and requires the intravenous administration of antiepileptic drugs [2,3]. If the ictal activity persists, anesthetics may be required to control refractory SE (RSE). In most severe cases, SE continues or recurs 24 h or more after the onset of anesthetic therapy (or recurs on the reduction or withdrawal of anesthesia). Such condition has been termed super-refractory SE (SRSE) [4] and represents an uncommon but important clinical condition with very high mortality and morbidity [4,5], where various pharmacological and nonpharmacological therapies are applied, most often without any evidence from clinical studies. In a recent population-based study, the incidence of RSE was 7.2 (95% confidence intervals [CI]: 3.3–13.8), whereas that of SRSE was 1.2 (95% CI: 0.1–5.1)/100.000 adults/year [5]. We recently reviewed the current experience with vagal nerve stimulation (VNS) in RSE and SRSE and found a 74% response rate for abrogation of SE [6].

In this narrative review, we present the currently available evidence supporting the use of neurostimulation, including VNS, direct cortical stimulation, transcranial magnetic stimulation, electroconvulsive therapy, and deep brain stimulation (DBS), to treat RSE and SRSE after failure of medical interventions.

2. Historical background

The birth of neurophysiology dates back to the seminal studies conducted by the Italian physician and physicist Luigi Galvani (1737–1798), who observed how application of electricity to dead frogs led to muscular movements. Results of his observations were reported in the famous treatise "*De viribus electricitatis in motu musculari commentarius*" (Commentary on the effects of electricity on muscular motion), published in Bologna in 1791 [7].

In 1803, the Italian scientist Giovanni Aldini (1762–1834), nephew of Galvani, demonstrated the efficacy of electricity in the body of Georg Foster, who had been executed for murdering his wife and child

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by drowning them in Paddington Canal, London. Aldini stimulated Foster's corps with electric current and, according to a record of the experiment, "On the first application of the process to the face, the jaws of the deceased criminal began to quiver, and the adjoining muscles were horribly contorted, and one eye was actually opened. In the subsequent part of the process, the right hand was raised and clenched, and the legs and thighs were set in motion" [8]. This public demonstration of the electrostimulation technique led to an increased interest towards "Galvanism", which culminated in the publication of the famous novel "Frankenstein; or, The Modern Prometheus" (first edition 1818) by the English writer Mary Shelley (1797–1851).

The electrical excitability of the brain was subsequently demonstrated by Gustav Theodor Fritsch (1838–1927) and Eduard Hitzig (1838–1907), who stimulating the cortex of live dogs and observing movements on the contralateral muscles, provided experimental evidence of a motor area in the cortex [9]. Their original experiments would later be replicated by David Ferrier [10]. The first who used electrical stimulation in living humans was the American physician Roberts Bartholow (1831–1904); he conducted a series of experiments on Mary Rafferty, who suffered from a deleterious epithelioma using faradic stimulation: unfortunately, the woman had several seizures after increase of stimulation strength and fell into coma, dying a few days later [11].

Electrical stimulation of the human cortex in patients with epilepsy was systematically investigated by Wilder Graves Penfield (1891–1976) and Herbert Jasper (1906–1999), and led to the identification of distinct cortical areas with specific functions. More specifically, electrical cortical stimulation in patients with epilepsy provided extremely valuable information. The technique currently known as "electrocorticography" revealed that (1) electrical stimulation of the cortex can silence down periodic spiking, (2) local stimulation may have distant effects in an epileptogenic network, and (3) electrical stimulation may ignite or interrupt seizures [12]. The demonstration that neocortical stimulation could interrupt seizures settled the basis for the clinical use of neurostimulation in epilepsy. The pilot studies with thalamic, subthalamic, neocortical, and hippocampal stimulation date back to the 1990's and eventually led to the approval of vagal nerve stimulation (VNS) for the treatment of epilepsy (1996). In subsequent years, thalamic stimulation (2010), trigeminal nerve stimulation (2012), responsive neurostimulation (RNS) (2013), and hazard ratio-responsive (HR-responsive) VNS (2014) were also approved for clinical use.

3. General remarks and biological principles

Stimulation of brain tissues is by far more complex than that involving single neurons and their axons. This is due to surrounding tissue properties, orientation of axons, electrolytes type of stimulation, field distribution, and many other factors, which can determine the biological effect on neuronal networks. Hence, although on the one hand electrical stimulation can lead to predictable responses at individual nerve fiber or axon level, such predictability is lost when stimulating the neuronal tissue – which comprise elements with different excitability properties such as soma and dendrites. Consequently, fields of distribution of currents can only be estimated, and net effects cannot be classified simply as excitatory or inhibitory, also because biological effects close to the electrode may be different from those further away [13].

Besides these biological issues, there are clinical ones that should be considered: acute interruption of seizures is different than prevention of seizures [14] or prevention of epileptogenesis [15], and mechanisms underlying SE (especially its later stages) may be fundamentally different than those responsible for single seizures [16]. Hence, SE has its own peculiarities which need to be taken into account.

4. Experimental evidence

In spite of the abundant use of neurostimulation in humans, there is still a striking shortage of a deep understanding of the mechanisms of neurostimulation, as well as good experimental data, which inform clinical studies. In this section, the key findings of experimental data are given in brief. Studies gathered from animal models have shown that different neurostimulation techniques (VNS, trigeminal nerve stimulation, electroconvulsive therapy) can modulate widespread brain networks but can also affect the activity of selective network nodes (Fig. 1). Hence, the site of stimulation plays a crucial role in the resulting anticonvulsant or proconvulsant effect [17] (Table 1).

In a seminal study, Woodbury et al. found that VNS was able to reduce the severity of maximal electroshock seizures in rats, by abolishing the extensor component of the tonic phase; furthermore, it proved effective in shortening or preventing tonic seizures induced by pentylenetetrazol [18,19]. A subsequent study in Wistar rats showed that VNS with square pulses (0.5 ms) at Hz 0.01 to 1.2 mA for 20 s reduced interictal spike frequency by 33% during and the effect lasted ≤3 min [20]. When the electrical stimulation was applied at seizure onset, there was a significant reduction of seizure duration, whereas stimulation starting more than 3 s after onset failed to control seizures. The inhibition of experimental seizures by repetitive VNS was also subsequently demonstrated in the 1990ties in a canine model of epilepsy [21]. This study allowed to identify the optimal stimulus parameters to control seizures (strength, approximately 20 V; electrode resistance, 1 to 5 Ω; frequency, 20 to 30 Hz; duration, approximately 0.2 ms), and provided further evidence that VNS can exert an anticonvulsant effect following the stimulation of small-diameter afferent unmyelinated fibers.

A marked suppression of network excitability with high-frequency stimulation following DBS was demonstrated in a sheep model of epilepsy [22]. After stimulating (30 s, at 6 V), the anterior thalamic nucleus raw local field potential (LFP) responses were recorded. The averaged evoked potentials were elicited by different stimulation amplitudes showing a graded input–output response; furthermore, averaged evoked potentials were elicited by different stimulation burst frequencies. Different DBS stimulation burst frequencies had different effects on LFPs recorded in the hippocampus. Hence, stimulation of these brain regions produced evoked potentials that were dependent on stimulus location and parameters. The effects of different burst frequencies of thalamic stimulation (10-s burst) on penicillin-induced spiking were investigated. High-frequency thalamic DBS produced a clear inhibition of epileptiform activity in the hippocampus which far outlasted the duration of the stimulation. These findings supported a potential therapeutic mechanism for DBS in the treatment of epilepsy.

As these studies clearly show, stimulus parameters especially frequency, polarity, and shape have a profound impact on the effect of the stimulation.

Ideally, clinical trials should be based upon a solid foundation of experimental work documenting the basis for a therapeutic effect and the optimal parameters for producing such an effect. However, much of the clinical work in neurostimulation is only loosely based on fundamental principles derived from experimental work. Hence, clinical trials were performed (in part successfully) with limited understanding of the basic mechanism underlying neurostimulation.

5. Current evidence for neurostimulation in status epilepticus

Several neurostimulation techniques are currently available for the treatment of epilepsy (Fig. 2), but the evidence supporting their use for the treatment of SE is sparse and of low quality.

5.1. Vagal nerve stimulation

Vagal nerve stimulation involves intermittent electrical stimulation of the left cervical vagus nerve by means of an implanted helical electrode connected to a pulse generator. Negative electrode generates action potentials that travel afferently via sensory fibers, whereas efferently traveling action potentials are mostly blocked by the positive

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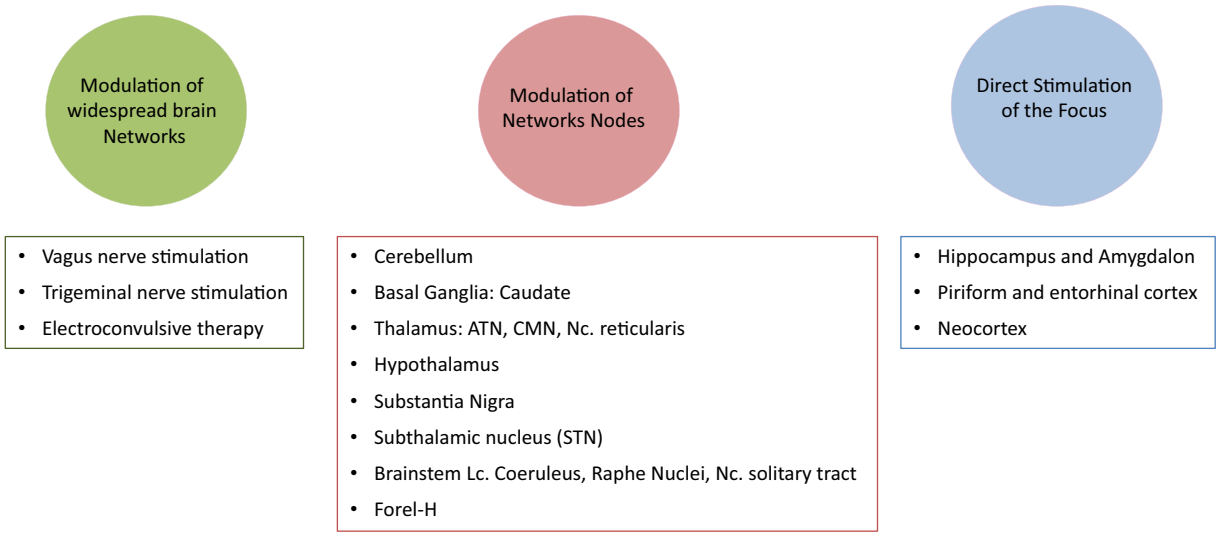

Fig. 1. Types and localisation of brain modulation in seizures and Status epilepticus.

electrode. Potentials that are not blocked could cause adverse effects. The therapeutic efficacy of VNS appears to be mediated by the activation of fast myelinated fibers in the vagus nerve [23]. Its anticonvulsant effect can be explained by several mechanisms, such as the modulation of neurotransmitter expression with increased inhibition and reduced excitability [24], changes in cerebral blood flow [25], desynchronization of electroencephalographic (EEG) rhythms [26], and antiinflammatory effects mediated by norepinephrine [27] (Fig. 3).

Clinical studies established the efficacy of VNS in patients with epilepsy. Five randomized trials conducted in a total of 439 patients with focal drug-resistant epilepsy were included in a Cochrane systematic review, comparing different types of VNS stimulation therapy [28]. The overall risk ratio for 50% or greater reduction in seizure frequency was 1.73 (95% CI: 1.13 to 2.64) for high-frequency VNS compared to low-frequency VNS (moderate quality of evidence); the risk ratio for treatment withdrawal was 2.56 (95% CI: 0.51 to 12.71; low quality of evidence).

The electrophysiologic effects of VNS on the human hippocampus and mesial temporal lobe structures were definitely demonstrated using intracranial depth electrodes in a patient undergoing presurgical evaluation for drug-resistant epilepsy [29]. Epileptiform activity was recorded from depth electrode left hippocampus (interictal spike frequency), and spike frequencies before and during VNS at 5- and 30-Hz were investigated. The anticonvulsant effect was strictly dependent on the stimulation frequency, as 30-Hz stimulation led to a significant decrease, whereas the 5-Hz stimulation was associated with a significant increase in epileptiform activity.

The use of VNS or other neurostimulation techniques is currently listed among the options for the treatment of SRSE, particularly after the failure of ketamine, magnesium, immunotherapy, and hypothermia or ketogenic diet [2,3]. Perhaps not surprisingly, in the preliminary results of a global audit of treatment of RSE, only a very few cases were treated with either VNS (3 out of 347, 0.9%), electroconvulsive therapy (1 case, 0.3%), or transcranial magnetic stimulation (1 case, 0.3%) [30].

Very recently, a systematic and comprehensive review of the literature has been performed to assess the efficacy of acute VNS implantation for the treatment of SE [6]. Overall, 43 patients with various etiologies of RSE or SRSE were included. Although cessation of SE was 67% and long-term seizure reduction 49%, results should be interpreted with caution for the high risk of publication bias (evidence level IV). However, the tolerability of acute VNS for SE appears to be good, with only 2 reported patients with bradycardia and 1 with seizure aggravation, and none with perioperative complication.

Some issues remain open with regard to the use of acute VNS implantation for SE. Optimal stimulation paradigms, timing of the acute implantation, and potential synergies with pharmacological agents should be further investigated. The role of age and etiology should also be assessed, considering that concomitant drugs could make it difficult to isolate the response of VNS from natural history (e.g., patients

Table 1
Diversity of effects of brain stimulation in animal models.
(Adapted from ref. [7]).

Site of stimulation	Anticonvulsant effects	No effects	Proconvulsant effects
Cerebellum	Deep nuclei and superficial: cat, rabbit, rat	Monkeys (electrical stimulation)	Cat (cobalt), rat, cat (penicillin)
Caudate	Cat, monkey		Rabbit, cat (penicillin)
Substantia nigra	Rat (3,4-AP, flurothyl), cat (penicillin)	Older cat (flurothyl)	Rat (Hc. stimulation, GAERS)
Subthalamic nucleus	Rat (flurothyl, GAERS)	Rat (flurothyl)	
Brainstem	Lc. coeruleus: rat (PTZ, penicillin, kindling), raphe: rat (PTZ, kindling), Nc. tractus solitarius.: cat		Dorsal raphe nucleus: rat (kindling)
Hypothalamus	Rat (focal carbachol, PTZ)		Rat (low frequency stimulation)
Ant. Nc. of thalamus	Rat (PTZ, Hc. kainate, pilocarpine)	Rat (low frequency stimulation, PTZ)	Rat (kainic acid)
Hippocampus/amygdalon	Rodent Hc. slice preparations	Rodent Hc. slice preparations	Kindling and evoked seizures
Piriform cortex	Rat (delayed kindling, low frequency stimulation)		Kindling in rodents
Neocortex	Cat (undercut model), rodent (slice)		Evoked seizures multiple species

Abbreviations: Ant.: anterior; GAERS: Genetic Absence Epilepsy Rats from Strasbourg; Hc.: hippocampus; Lc.: locus; Nc.: nucleus; PTZ: pentylenetetrazole; 3,4-AP: 3,4-aminopyridine.

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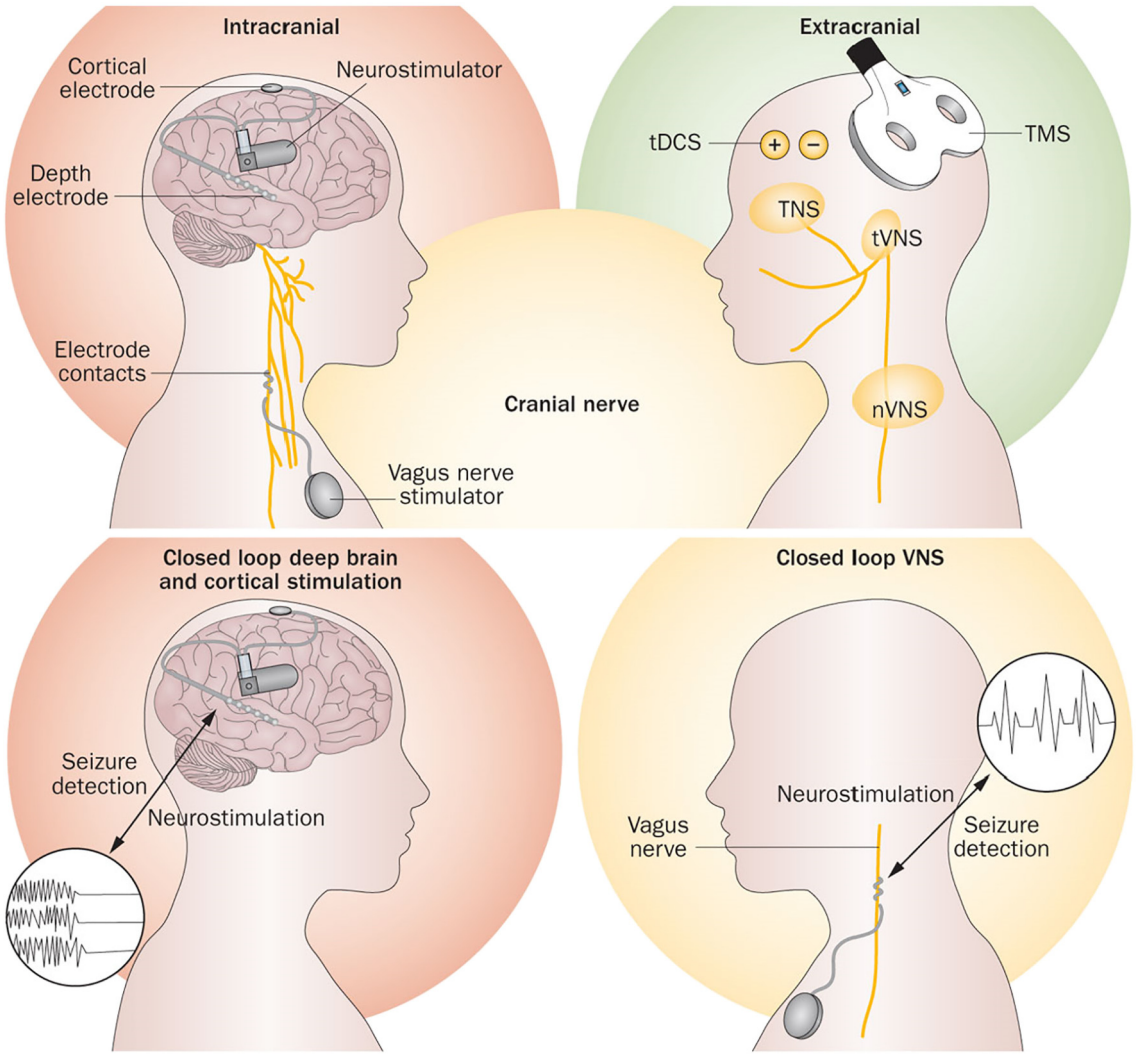

Fig. 2. Types of neurostimulation techniques and targets used for patients with epilepsy.
(Reproduced with permission from: Vonck K, Boon P. Epilepsy: closing the loop for patients with epilepsy. Nat Rev. Neurol. 2015;11:252–4).

with N-Methyl-d-aspartate (NMDA) encephalitis also receiving immune therapy). Finally, the time to clinical response, and stimulation parameters should be recorded carefully in a standardized way, to allow conclusions on a possible causal relationship between VNS and SE cessation.

5.2. Responsive neurostimulation

Responsive neurostimulation aims to suppress ictal activity by delivering stimulation directly in response to electrographic activity; as such, it can be targeted to the specific brain regions involved in the seizure and is time-specific, as stimulation is provided only when needed [31]. The NeuroPace RNS System, an implantable responsive neurostimulator system was evaluated in a multicenter, randomized, double-blinded trial for the treatment of drug-refractory epilepsy [32]. During the 12-week study period, seizures were significantly reduced in the treatment compared to the sham group (−37.9% versus −17.3%; $p = 0.012$), with no difference between the groups in adverse events. Overall quality of life was also significantly improved ($p < 0.02$) without deterioration in mood or neuropsychological function.

So far, only one case of RNS being used to treat a case of SE was reported [33]. It was a 37-year-old man with drug-resistant focal epilepsy due to cortical dysplasia in motor cortex who developed SRSE. Detection and stimulation parameters were adjusted over a 14-day period using RNS (Neuropace®), and SE ceased 15 days after implant, with return to neurological baseline status at 6 weeks of follow-up. However, "ketamine infusion was started the day after this stimulation change as pentobarbital infusion was weaned, and all IV anesthesia was discontinued 96 h later". Hence, because of the change in concomitant medications, it is not possible to establish a strong causal relationship between RNS and SE cessation.

5.3. Direct cortical stimulation

So far, 8 patients (1 with RNS) with RSE of various etiologies (mostly *epilepsia partialis continua* or focal motor SE) have been reported, with successful implantation in 7/8 patients and seizure control in 87% [34–37]. Data on long-term seizure reduction were not sufficiently described (the shortest follow-up was 6 weeks). No adverse effects were reported.

As for VNS, also for the use of direct cortical stimulation, there are still some open issues: the stimulus parameters used so far in SE are empiric and need validation and standardization in larger case series with less clinical heterogeneity (particularly with regard to etiology and age); time to response and effect of concurrent treatments should be collected prospectively to assess the clinical response.

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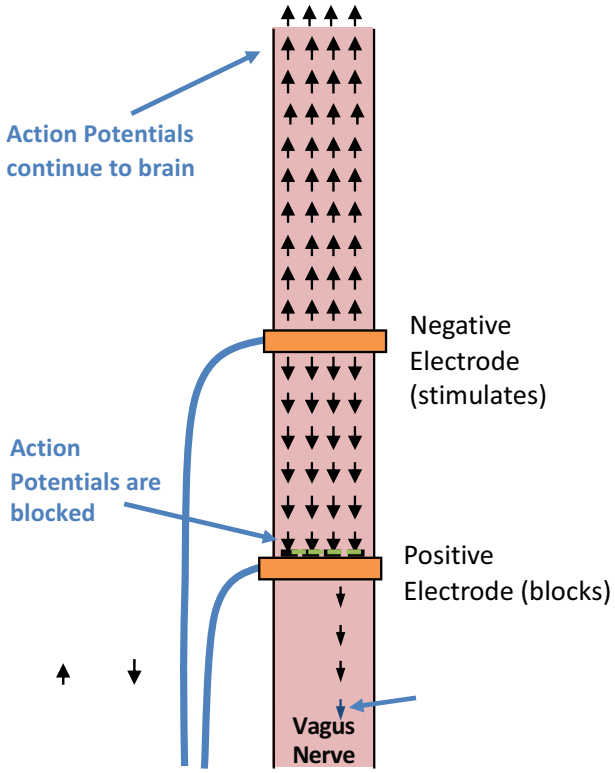

Fig. 3. Mechanisms underlying the anticonvulsant effect of VNS therapy.

5.4. Deep brain stimulation

Overall, 4 patients with RSE of different etiologies (1 absence SE in juvenile absence epilepsy; 1 common variable immunodeficiency-associated encephalomyelitis; 2 cases of unknown cause) treated with intracranial neurostimulation have been reported so far. Three patients underwent electrical stimulation of the centromedian thalamic nuclei [38–40] and one of the anterior nucleus of the thalamus [41]. Although successful implantation occurred in 3 of 4 patients and seizure control in 75%, long-term seizure reduction was not sufficiently reported. No adverse effects were reported for implantation in SE cases; however, the occurrence of SRSE was reported in a patient following DBS implantation for treating Parkinson's disease [42].

5.5. Repetitive transcranial magnetic stimulation

Overall, 23 patients with various etiologies of SE and RSE have been reported with different types of stimulation (low and high frequency) [43]. Success rate was 43.5% with relapse occurring in 76.5%, and long-term outcomes (>6 months) not reported.

5.6. Transcutaneous direct current stimulation (tDCS)

Evidence on the use of transcutaneous direct current stimulation (tDCS) in SE is anecdotal. In animals, pilocarpine-induced SE in immature rats treated with tDCS was associated with 21% reduction in convulsions on postnatal day 55 [44].

A case report described the effect of tDCS in a 20-years-old woman with *epilepsia partialis continua* involving the left hand; tDCS (administered at 2 mA for 20 min with cathode over C4) led to complete cessation of *epilepsia partialis continua*, but involuntary movements gradually reappeared [45]. The efficacy of tDCS was reported also in a previously healthy teenager who presented with de novo *epilepsia partialis continua* and metabolic stroke resulting from the homozygous p.Ala467Thr POLG mutation [46].

However, in a controlled study, 5 patients with focal, refractory continuous spikes and waves during slow sleep underwent cathodal tDCS or sham stimulation before sleep (1 mA; 20 min) in 5 successive sessions [47]. Cathodal tDCS did not reduce the spike index in any of the patients.

5.7. Electroconvulsive therapy

The use of electroconvulsive therapy in psychiatry was proposed in 1934 by Ladislas Joseph Meduna as a treatment for major depressive disorder, mania, and catatonia [48]. The goal of electroconvulsive therapy for treating psychiatric disorders is to elicit seizures and, consequently, to allow withdrawing medication. The placement of electrodes, as well as the dose and duration of the stimulation is determined on a per-patient basis, and short-acting anesthetics such as methohexital, etomidate, or thiopental are given, together with a muscle relaxant such as suxamethonium (succinylcholine), and occasionally atropine to inhibit salivation [48]. Brief pulses of electrical stimulus with 800 mA (up to several hundred watts) induce current flows for 1 to 6 s. The mechanism underlying the clinical effects of electroconvulsive therapy, including its potential efficacy in terminating SE, is poorly understood. Its adverse effects include retrograde amnesia, anterograde amnesia, confusion, and permanent memory changes.

So far, 27 patients with SE of various etiologies undergoing electroconvulsive therapy administered according to psychiatric standard protocols have been reported, with a success rate of 59% [49,50]. The most frequent adverse effects include transient lethargy or amnestic episode, or confusion; no cardiac arrest or death has been reported.

6. Conclusions and future directions

So far, neurostimulation has been investigated in few cases of RSE and SRSE (VNS: 43; electroconvulsive therapy: 27; repetitive transcranial magnetic stimulation: 23; direct cortical stimulation: 8; DBS: 4), with various success rates (43.5% repetitive transcranial magnetic stimulation; 59% electroconvulsive therapy; 67% VNS; 75% DBS; 87% direct cortical stimulation). In all of the published studies, publication bias is likely to have affected the efficacy results, and poor reporting prevents drawing robust conclusions. Noninvasive neurostimulation (tDCS) appears to be ineffective or to have very low efficacy against SE. On the other, the different neurostimulation techniques discussed above have been remarkably well tolerated, with no systemic effects, or procedure- or device-related complications.

Future directions of neurostimulation for the treatment of SE include the investigation of neuronal targets so far unexplored (e.g., cingulate gyrus, amygdala, entorhinal cortex, Forel H-field), adopting new stimulation algorithms and parameters [51]. A more targeted selection of patients and a prospective collection of data from more clinically homogeneous populations and longer follow-up will improve our understanding of the acute and chronic effects of neurostimulation. This will proceed in parallel with the development and implementation of better devices (electrodes, stimulators, cables) and technological improvements. Multicenter prospective observational studies and device registries with standardized reporting are required to further assess the efficacy of different neurostimulation techniques for the treatment of SE.

Declaration of competing interest

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member of the following ILAE Task forces: Medical Therapies, Nosology, Terminology, Congresses, Driving, Regulatory affairs, and Telemedicine.

Dr. Brigo received travel support from Eisai; he acted as consultant for Eisai, LivaNova, and UCB Pharma; and he serves on the editorial board of the journal Epilepsy & Behavior, is Co-Chair of the ILAE Guidelines Taskforce, and editor of the Cochrane Epilepsy Group.

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