



Intracranial and epicranial focus stimulation—concepts and approval status—English Version

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Abstract

Stimulation of epileptic foci targets the modulation of seizure generation at its source. Experimental studies show the efficacy of high-frequency stimulation to reduce epileptic activity and seizures originating in the hippocampus. In humans, a number of small series of hippocampal stimulation have shown variable results. In the US, responsive neurostimulation with electroencephalogram (EEG)-triggered high-frequency stimulation achieved a reduction of median seizure frequency by 38% after 3 months, by 43% after 12 months, and by 56% after 24 months of treatment. In Europe, epicranial focal cortex stimulation has reduced the median seizure frequency by >50% after 6 months of combined high-frequency and direct current (DC)-like stimulation. Given their good cognitive and general tolerability, either approach reasonably complements therapeutic approaches in pharmacoresistant focal epilepsy.

Keywords

Neurostimulation · Responsive neurostimulation · High-frequency stimulation · Focal cortex stimulation · Seizure detection

Background

Neuromodulatory procedures are applied in epilepsy treatment using highly heterogeneous targets and associated mechanisms of action [35]. For example, the first method of vagus nerve stimulation approved for clinical epilepsy treatment uses electrical stimulation of a cranial nerve to achieve a reduction in seizure tendency via activation of afferent fibers. According to current understanding, activation of the nucleus of the solitary tract [21] and the dorsal raphe nuclei [22] causes a diffuse release of noradrenaline and serotonin, with modulatory effects on limbic areas as well as the thalamus, hypothalamus, and insular cortex [14].

By contrast, the second method of stimulation of the anterior thalamic nuclei to be approved in Europe—deep brain stimulation of the anterior nuclei of the thalamus (ANT-DBS)—stimulates thalamic nuclei areas that are considered relevant for the propagation of epileptic activity, es-

pecially during temporal generation [12, 32]. According to current understanding, the high-frequency stimulation used here (typically at 145 Hz according to the SANTE study protocol) reduces the recruitability of the anterior thalamic nuclei, the Papez circuit, and mesial frontal projection areas.

A completely different approach is taken when the region of seizure origin, the epileptic focus, is made the target of neurostimulation. In this case, the primary goal is not to modulate extensive networks but to directly change the epileptogenicity of the focus or alternatively achieve early suppression of seizure patterns that have developed.

The following is a review of animal models in which focal stimulation has been studied, human experimental studies of hippocampal stimulation, and two focal stimulation procedures approved in the United States and Europe, respectively.

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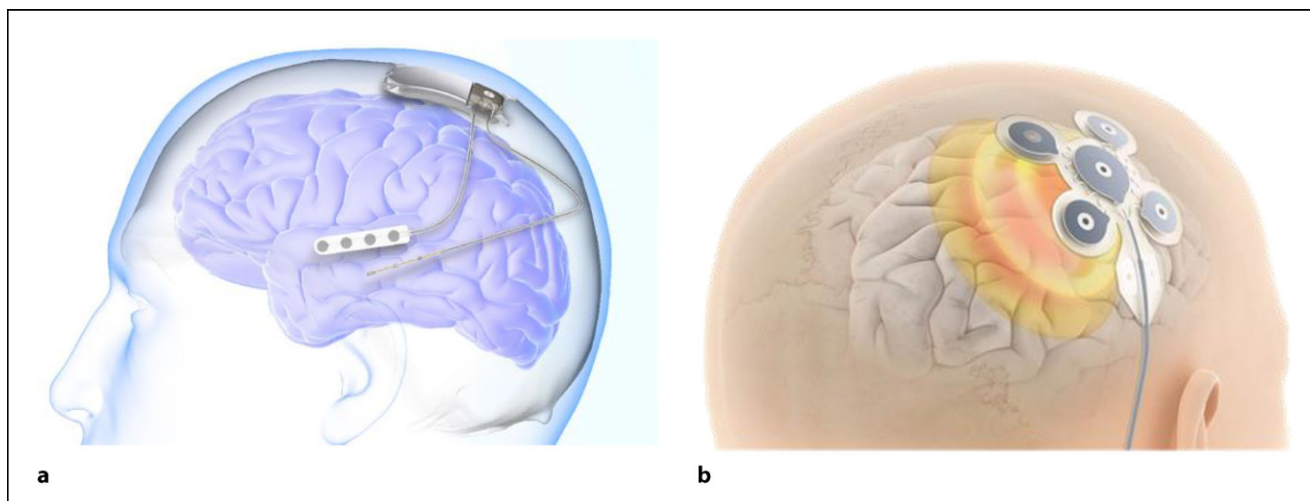


Fig. 1 ▲ The responsive neurostimulation (RNS) implant (a) and the epicranial focal cortex stimulation (FCS) electrode (transcranial focal stimulation; b). In RNS, the generator and four-channel subdural or depth electrodes are placed intracranially for EEG recording and stimulation; in FCS, stimulation is delivered epicranially over the focal area via a five-channel electrode with a Laplacian design

Animal-based approaches to modulating the activity of epileptic foci

Neurostimulation approaches for anticonvulsant therapy of epileptogenic foci have been experimentally evaluated largely in the hippocampus. This involves both in vitro studies of seizure suppression in hippocampal slices and in vivo studies of treatment in chronic epilepsy models [11].

Different forms of stimulation were evaluated in vivo in the hippocampus. Low-frequency stimulation (1–10 Hz) resulted in reduced seizure frequency or seizure severity, reduced duration of after-discharges, or increased threshold to trigger seizures in kindling models. In chemical models (kainate/4-AP), reduced seizure frequency or bilaterally reduced epileptic activity was also achieved [11]. Not all studies found a reduction in seizures—in some cases only a reduction in interictal activity was found [4].

High-frequency stimulation (50–185 Hz) also had an effect on epileptogenesis in the form of a blockade of the kindling process at stage II–III in animal experiments in the kindling model [6] or increased the threshold for triggering after-discharges and shortened them. In chemical models to establish epileptic foci, radiofrequency stimulation led to a reduction in seizure frequency or complete seizure suppression.

Direct current (DC) stimulation has also been used to suppress epileptic activity. Its effect depends largely on the geometric relationships between the orientation of the neurons and the externally applied field. The DC fields, as shown in slice experiments, can effectively suppress epileptic activity here [3, 9, 28]. The noninvasive transcranial DC studies on cathodal stimulation in humans based on this approach are presented in a separate article [18].

Human hippocampal stimulation studies

To date, human studies of hippocampal stimulation have been conducted using only radiofrequency stimulation, with the exception of one brief study during invasive monitoring. A review by Han [11] reports heterogeneous results from 18 mainly uncontrolled studies, each with a maximum of 12 participants treated by implanted open-loop deep electrodes with a stimulation frequency of 130–200 Hz. Only one study reported (reversible) cognitive side effects. In total, 41 of 55 (75%) of the presented patients who underwent hippocampal radiofrequency stimulation achieved >50% seizure reduction, while 15 of 55 (27%) had a seizure reduction of at least 90% over highly variable observation periods ranging from 2 weeks to 30 months.

Similarly, a double-blind study showed a responder rate of 69% [42], while other studies comparing groups on vs. off stimulation only showed differences in seizure frequency of 15–33% [27, 40]. Therefore, further studies with larger patient cohorts are needed to provide better evidence for this interesting therapeutic approach.

Responsive neurostimulation of epileptic foci

In the United States, a method for stimulating epileptic foci using subdural or depth electrodes and a generator implanted in the skull has been approved since 2011 (■ Fig. 1a). The generator not only performs electrical stimulation via electrodes implanted in the focal area but also continuously analyzes the intracranial electroencephalogram (EEG) registered in the focal area and performs stimulation triggered by seizure pattern detection. The primary goal here was to interrupt seizure patterns at an early stage.

A randomized, prospective, double-blind study of 191 patients demonstrated significant superiority for EEG-triggered stimulation vs. implantation without activated stimulation [29]. Implantation resulted in an insertion effect with an approximately 25% seizure reduction; over a 3-month observation period, seizure reduction was 37.9% in the stimulation group vs. 17.3% in the group with sham

stimulation throughout the stimulation period, and 41.5% in the stimulation group vs. 9.4% in the sham group during the last month of treatment. In the open-label, unblinded long-term follow-up, median seizure reduction improved to 44% at 1 year and 53% at 2 years [2, 17], an effect that was stable over the further course or that even increased in the subgroup of patients continuing treatment, with a 75% reduction in median seizure frequency [30].

Effectiveness was assessed separately for mesial temporal stimulation [8] and neocortical stimulation, with evidence of effectiveness for both localizations and different etiologies [39].

Perioperative morbidity was low, involving headache at the implant site, but device infection occurred in 5% of patients, and the infection rate increased to 12.1% over the long term [17]. Another paper describes an infection rate of 3% per patient-year following implantation [8]. Direct stimulation-related side effects were not observed. The first-generation generators needed to be surgically replaced after approximately 4 years, while the currently used follow-up generation is expected to have a lifetime of 8 years.

Three algorithms are used for seizure detection (line length, half wave, and area), and thresholds are set individually by the treating physician, for example, taking into consideration knowledge of the predominant seizure frequency to include half-wave detections [33]. The detection parameters were chosen to be exceedingly sensitive in the pivotal study, resulting in a mean frequency of over 1000 stimulations/day [13, 17]. Stimulation is mostly by means of short (100 ms) and high-frequency bursts of 200-Hz stimulation frequency at amplitudes in the range of 1–4.5 mA; stimulation of adjacent contacts and inter-electrode stimulation to modulate larger areas are possible [17, 33]. Despite the high number of triggered stimulations, the total duration of stimulation is approximately 6 min/day, which is significantly less than open-loop stimulation approaches.

The role of the originally intended mechanism of seizure interruption for the therapeutic effect has been insufficiently demonstrated to date (cf. Hirsch

[16] in this issue). One study even reported a higher effectiveness for open-loop stimulation compared to the usual closed-loop approach [41]. A case report showed that even in patients with seizure patterns visible in surface EEG and not interrupted by ictal stimulation, switching the stimulator off and on reproducibly resulted in a reduction of seizure frequency [5]. The gradual trend in seizure reduction over a period of months to years, apart from the insertion effect, further indicates that a long-term and gradual neuromodulation of seizure generation in the focus occurs. A recent EEG analysis further found that a progressive, frequency-dependent reorganization of interictal functional connectivity predicts the effectiveness of responsive neurostimulation (RNS; [19]). Similarly, EEG analyses found an effect solely on parameters such as interictal inhibition, frequency modulation, and fragmentation, with a positive outcome correlated only indirectly and in the interictal period with RNS effectiveness [20].

Recent data suggest that lower frequency stimulation at 7 Hz can also produce seizure reduction, again supporting a neuromodulatory effect for RNS [1].

To date, the manufacturer, NeuroPace (Mountain View, CA, USA), has obtained only FDA certification for its RNS system, thus it is not yet available in Europe.

Epicranial focal cortex stimulation with the EASEE system

An implantable device for the stimulation of epileptic foci recently became available in Europe, consisting of a generator in the chest region and an epicranial electrode array fixed over the epileptic focus (from [37]; ■ Fig. 1b). The device, named EASEE (epicranial application of stimulation electrodes for epilepsy; Precisis GmbH, Heidelberg, Germany), has an electrode with a diameter of 5 cm and a design similar to a Laplacian electrode with four outer electrodes placed on an outer ring around a central electrode. This allows for improved penetration of electrical fields when individually adapted to the geometry of the skull [10]. Modeling suggests relevant effects on neuronal activity in the region of gyral crests of dorsolateral con-

vexity at stimulation intensities of 1–2 mA [24, 31].

The device enables the use of different stimulation modes that can be applied in a time-programmed manner. In particular, these include high-frequency stimulation (up to 200 Hz), low-frequency stimulation (from 0.3 Hz), and DC-like stimulation, which has been used for epilepsy treatment in the form of up to 20-ms-wide cathodal pulses and compensatory low-amplitude anodal compensating pulses [26, 34, 43–45].

In two prospective, unblinded studies of the tolerability and efficacy of focal cortex stimulation (FCS; EASEE-II, PIMIDES-I, [23]), 32 patients underwent combined stimulation using 100 Hz for a duration of 6 min/day, spread over the day, and DC-like stimulation with broad subthreshold cathodal stimulations for a duration of 20 min/day. In addition to this, patients in the PIMIDES-I study were also able to trigger high-frequency stimulations in the seizure when they noticed the seizure using a hand-held device given to them. To be included, patients had to be pharmacoresistant and have a predominant epileptic focus (EEG information was sufficient for this; the presence of a lesion was not a prerequisite for study inclusion).

A joint analysis of the two studies showed good tolerability of implantation and stimulation. Regarding efficacy, in contrast to procedures with intracranial stimulation, electrode implantation had no insertion effect on seizure frequency; this reflects the extracranial positioning of the stimulating electrode. Initial analyses after a stimulation period of 6 months have recently been published, showing a gradual onset of reduction in seizure frequency, with half of the treated patients being responders with a seizure reduction by >50% [34, 38]. A positive effect for stimulation was shown on different seizure types.

Currently, most patients are undergoing long-term follow-up to document the long-term efficacy and tolerability of the treatment, particularly on the issue of stability of seizure control and possible further improvements over time, as described for RNS as well as other stimulation methods [30, 36]. The open treatment setting will also make it possible to investi-

gate modified stimulation parameters (isolated high-frequency stimulation/DC-like and low-frequency stimulations) and to identify individually effective stimulation parameters.

The number of study participants in the unblinded FCS studies ($n = 33$) was smaller than in published pivotal studies of other neurostimulation methods. Nevertheless, comparing these open treatment data with the blinded pivotal studies of vagus nerve stimulation, thalamic stimulation, and RNS, as well as published follow-up studies under open treatment, a treatment effect comparable to that achieved with RNS and deep brain stimulation (DBS) after a treatment period of 1–2 years is obtained. This would be a remarkable result for a much less invasive procedure. The long-term stability of these data needs to be confirmed through ongoing long-term data collection. In September 2022, FCS treatment was CE-certified and is thus available in Europe.

The EASEE system currently only allows for open-loop stimulation with predefined stimulation parameters and patient-triggered stimulation during seizures. Individual cases indicate that ictal stimulation may also be effective [15]. The electrode used is in principle equally suitable for EEG recordings [7]. Further developments of the device could therefore also make it suitable for closed-loop applications based on seizure detection [25]. Corresponding developments are currently funded by the German state of Baden-Württemberg (GRANT Brain-MEP, BW1_1276/03).

Outlook

The approach of focal stimulation for the treatment of focal epilepsy shows good results in animal models as well as in the use of two FDA- and CE-certified implants even in highly pharmacorefractory patients. Whereas significant long-term results are already available for intracranial RNS, these are still awaited for FCS. Unfortunately, RNS is only available in the United States. Since the vast majority of patients receiving implants for epicranial neurostimulation have decided to continue treatment, long-term follow-up data will also become available in the coming year. If good efficacy is confirmed for the

less invasive epicranial focal stimulation, this would certainly be an interesting option for inoperable patients—or patients unwilling to undergo surgery—with an identifiable focal area.

Practical conclusion

- Neuromodulatory procedures are employed in epilepsy treatment using highly heterogeneous targets and mechanisms of action.
- Neurostimulation approaches for anticonvulsant therapy of epileptogenic foci have been experimentally evaluated largely in the hippocampus.
- Recently, an implantable device for the stimulation of epileptic foci has become available (the EASEE system: epicranial application of stimulation electrodes for epilepsy), which is fixed epicranially over the epileptic focus. The device enables the use of different stimulation modes that can be applied in a time-programmed manner.
- The approach of focal stimulation for the treatment of focal epilepsy shows good results in animal models as well as with the use of two FDA- or CE-certified implantable devices even in highly pharmacorefractory patients.

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Declarations

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No studies on humans or animals were performed by the authors for this article. For the studies listed, the ethical guidelines stated there apply in each case.

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