Neuromodulation for Epilepsy

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KEYWORDS

• Deep brain stimulation (DBS) • Intractable • Neurostimulation • Refractory seizures
• Trigeminal nerve stimulation (TNS) • Vagus nerve stimulation (VNS)

KEY POINTS

- Several neuromodulation options are available as palliative treatments for patients with medically refractory epilepsy.
- Vagus nerve stimulation, thalamic deep brain stimulation, and trigeminal nerve stimulation are currently the dominant nonresponsive treatment modalities in use.
- These different neurostimulation modalities all have a good safety profile and satisfactory rates of seizure reduction.

INTRODUCTION

A significant proportion of epilepsy patients is medically refractory,[1,2] and apart from those who are candidates for resective surgery, most will continue to have disabling seizures for rest of their lives.[3,4] Neuromodulation, or neurostimulation, is a palliative treatment option for many of these patients who are not eligible for resective surgery or who have persistent medically intractable refractory seizures despite previous epilepsy surgery.[5] Patients typically have partial onset seizures, with or without secondary generalization, or less frequently, generalized epilepsies. Candidates for neuromodulation usually have a long-standing history of intractable epilepsy and have undergone extensive investigations, including video-electroencephalography (EEG), advanced neuroimaging, and even intracranial subdural or depth electrode implantations for seizure localization in many cases. Most of these patients have been found to have no single discrete seizure onset localization; a minority has seizure onsets localized to nonresectable areas of eloquent cortex, for example, within the boundaries of language centers in the dominant temporal or frontal lobes.

Neuromodulation as an alternate form of treatment for intractable epilepsy was first considered based on historical observations that electrical stimulation of subcortical structures could modify the cortical EEG: high-frequency stimulation "desynchronized" the EEG and low-frequency stimulation "synchronized" the EEG.[6–9] Increased cortical synchrony mediated by low-frequency stimulation was demonstrated to be proepileptic, while cortical desynchronization mediated by high-frequency stimulation was shown to be antiepileptic.[10,11] Experimental or clinical antiepileptic

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properties were subsequently reported with chronic electrical stimulation of several different central and peripheral nervous system sites, including the cerebellum, hypothalamus (mamillary nuclei), vagus nerve, trigeminal nerve, caudate nucleus, substantia nigra, centromedian thalamus, anterior thalamus, subthalamic nucleus, and the amygdalohippocampal region.[12–44] In 1997, peripheral vagus nerve stimulation (VNS) was the first neurostimulation modality to be licensed for the treatment of patients with refractory epilepsy: controlled trials and subsequent widespread clinical usage have demonstrated significant, albeit modest, reduction in seizure frequencies.[45,46]

Following the successes of VNS, and with the hope that direct stimulation of central nervous system structures might provide additional, more robust, benefit in terms of seizure control, interest was renewed in performing clinical trials of deep brain stimulation (DBS) for epilepsy. The initial clinical trials of DBS in epilepsy were performed in the 1970s and 1980s, mainly using cerebellar and, to a lesser extent, thalamic or caudate stimulation.[12–16,21] DBS of the centromedian thalamic nucleus (CM) for intractable epilepsy was reported in several articles, with benefits in seizure control described in a most patients.[22–25,29]

The mechanisms by which DBS may control seizures are largely hypothetical and unproven. CM stimulation, acting via the widely projecting nonspecific thalamic system, is hypothesized to act through induction of cortical desynchronization, preventing seizure propagation and generalization.[22,29] Based on experimental data describing a "nigral control of epilepsy" system in rodents, controlled in large part by activity in the substantia nigra pars reticulata (SNpr),[47] subthalamic nucleus stimulation has been proposed to act through disfacilitation of SNpr neurons,[33] although there is no direct evidence for such a control system in primates. The anterior thalamus has been demonstrated to be involved in seizure propagation, both experimentally and clinically, and stimulation or lesioning of the anterior nucleus (AN) or its afferent pathways have been shown experimentally to have antiepileptic properties.[13,17–21] The dorsomedial nucleus of the thalamus, situated posterior and inferior to AN, has also been shown to be involved in the maintenance and propagation of seizures, specifically those involving limbic brain structures.[48,49] Anterior thalamus stimulation, aimed especially at AN, is thus hypothesized to act through blockade of corticothalamic synchrony, similar to CM. All of these proposed mechanisms are strictly hypothetical and, in fact, even the local effects of DBS are poorly understood. In a broad sense, most of the clinical effects of DBS can be considered to result from local inhibition of function, in that the effects are typically mimicked by lesions or application of inhibitory neurochemicals. Nevertheless, the mechanisms of local inhibition are unresolved, and it is possible that some effects of DBS could result from local neuronal or axonal excitation.

The exact parameters necessary to optimally alter the relevant corticothalamic networks with electrical stimulation are unknown, apart from the need for high-frequency stimulation (eg, $\geq$100 Hz). In the experimental models cited above, it is only high-frequency stimulation that shows antiepileptic properties, usually attributed to a cortical desynchronizing effect. In contrast, low-frequency stimulation tends to be proepileptic in experimental models, an observation conceptually linked to the increased synchronization in cortex that can be demonstrated through induction of the so-called recruiting rhythm with low-frequency thalamic stimulation.[6,10,11,50]

In general, neuromodulation therapies have excellent safety profiles, and stimulation can, at least theoretically, be titrated to optimize seizure control. However, neuromodulation is not expected to provide freedom from seizures or antiepileptic medications. The aim of these palliative treatment modalities is to either reduce seizure frequency or prevent secondary generalization in order to minimize the many risks associated with intractable epilepsy. At present, the primary neuromodulation modalities in use for the treatment of patients with medically refractory epilepsy are AN DBS, VNS, trigeminal nerve stimulation (TNS), and responsive neurostimulation (RNS) (**Fig. 1**).

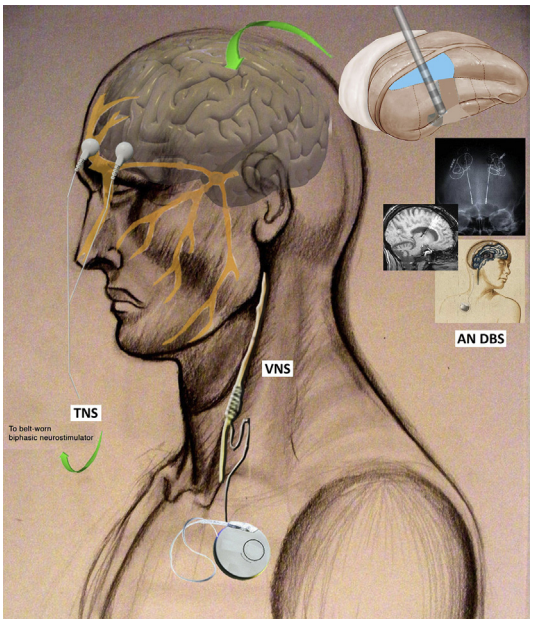

Fig. 1. Neuromodulation approaches.