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Neuromodulation for temporal lobe epilepsy: a scoping review

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Abstract

Temporal lobe epilepsy (TLE) is difficult to treat as it is often refractory to treatment. Apart from traditional medical treatment, surgical resection is also a choice of treatment, but it may be associated with significant cognitive deficits. As a result, treatment strategies using targeted and adjustable stimulation of malfunctioning brain circuits have been developed. These neuromodulatory therapies using approaches of electric and magnetic neuromodulation are already in clinical use for refractory epilepsy while others such as optogenetics, chemo-genetics and ultrasound modulation are being tested in pre-clinical TLE animal models. In this review, we conducted an in-depth literature search on the clinically available neuromodulatory approaches for TLE, focusing on the possible mechanism of action and the clinical outcomes including adverse effects. Techniques that are currently explored in preclinical animal models but may have therapeutic applications in future are also discussed. The efficacy and subsequent adverse effects vary among the different neuromodulatory approaches and some still have unclear mechanisms of action in TLE treatment. Further studies evaluating the benefits and potential limitations are needed. Continued research on the therapeutic mechanisms and the epileptic brain network is critical for improving therapies for TLE.

Keywords: Deep brain stimulation, Drug-resistant epilepsy, Neurostimulation, Vagus nerve stimulation, Transcranial direct current stimulation, Transcranial magnetic stimulation

Background

Epilepsy affects approximately 50 million people worldwide [1]. The International League Against Epilepsy defines epilepsy as "a condition characterized by two or more recurrent epileptic seizures over a period longer than 24 h, unprovoked by any immediately identified cause" [2]. Based on the seizure origin, epilepsy can be classified as generalized or focal-onset [2, 3]. Among the focal-onset seizures, temporal lobe epilepsy (TLE) is the most common, affecting 40% of adolescents and adults with epilepsy[1]. TLE can affect both lobes of the brain simultaneously, although there is often a predominant unilateral focus [3].

TLE is also one of the most common drug-resistant forms of epilepsy [4, 5], so its management remains challenging. TLE is often associated with underlying histopathological changes, predominantly hippocampal sclerosis (HS) [6], which has been associated with increased incidence of drug resistance [4, 6]. Patients presenting with drug resistance may benefit from surgery, which involves resection of part or the whole of the medial temporal structures [4]. However, even with resection, 30%–40% of patients with TLE do not show clinical improvement [5, 7]. Moreover, when the epileptogenic focus is bilaterally located or within a highly functional cortical area, resection may not be feasible [8]. Therefore, new treatment modalities are required to address the treatment gap.

While seizures are the most prominent clinical feature of epilepsy, individuals with TLE are at an increased risk of several comorbidities including cognitive dysfunction

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such as memory, attention, and behavioral deficits. Although the deficits in cognition are primarily linked to seizures, it has been found that aberrant electrical activity during the seizure-free period (inter-ictal activity) also plays a role in the cognitive co-morbidity [9]. Additionally, the inter-ictal electroencephalography (EEG) changes have been found to occur more commonly in TLE than in other epilepsies [10, 11], which is of great importance and needs further investigation in clinical management.

An improved understanding of epilepsy networks has led to the identification of new therapies, among these is neuromodulation. "Neuromodulation" is a reversible and efficient treatment alternative that alters the behavior of specific neural populations by targeted external or internal stimulation to the brain. Different methods of neuromodulation have been developed for the management of epilepsy, such as deep brain stimulation (DBS), transcranial direct current stimulation (TDCS), vagus nerve stimulation (VNS), and transcranial magnetic stimulation (TMS). These methods have been widely tested in randomized controlled trials among patients with refractory TLE [12–15].

In this review, we discuss the efficacy of these neuromodulatory approaches in the clinical management of refractory TLE. For each therapy, we provide the primary and secondary outcomes in clinical trials. We also review the application of neuromodulation in preclinical animal models and discuss their potential translation into human patients in the future.

Literature search

Literature search was made in PubMed, MedLine, and Clinicaltrials.gov, using the following search terms: "temporal lobe epilepsy," "seizures", and specific MESH term of the intervention: "deep brain stimulation" OR "transcranial direct current stimulation" OR "Vagus nerve stimulation" OR "transcranial magnetic stimulation". Randomized controlled trials, double- or single-blinded or unblinded or placebo-controlled studies on the intervention in patients with refractory TLE were selected. Patients were considered to be drug-resistant if they had uncontrolled seizures after adequate treatment for two years with at least two first-line antiepileptic drugs [16]. The search was restricted to human studies and to papers published in the English language. The reviewed papers were further extended to relevant articles in the references of each paper.

DBS

DBS involves direct electric stimulation of subcortical structures through stereo-tactically implanted electrodes controlled by a battery-powered pulse generator to therapeutically alter the neural function. DBS has shown great promise in improving motor function in dystonia, Parkinson's disease and Tourrett's syndrome [17, 18]. The success has extended its use beyond the treatment of movement disorders to the treatment of psychiatric disorders such as depression [19] and obsessive–compulsive disorder [20]. DBS has also been applied to treat various forms of seizure disorders, from primarily motor seizures to absent seizures, and generalized and focal forms of epilepsy such as TLE [21]. In epilepsy, a DBS system is integrated with sensing electrodes that detect seizures and deliver electric stimulation only when required, creating a "closed-loop stimulation".

Mechanism of action

The mechanism by which neuromodulation acts in DBS is poorly understood. However, earlier research shows that the effects are inhibitory in nature. Studies have shown that stimulation of the subthalamic nucleus results in suppression of neuronal activity in both patients with Parkinson's disease [17] and animal models [18]. This led to the introduction of the "inhibition hypothesis" [19], which suggests that the inhibition of the epileptic focus is attributed to the block of depolarization or inactivation of voltage-gated ion channels [20–22]. The effects of DBS are comparable to those of ablative surgeries such as pallidotomy and thalamotomy. Some studies also suggest that the micro-lesions produced during electrode implantation and stimulation could explain the way DBS reduces seizures [20, 23, 24]. Another explanation for neural inhibition by DBS is the increased levels of gamma-amino butyric acid (GABA) and up-regulated expression of GABA-B receptor during and after stimulation [20, 25].

The outcome and efficacy of DBS are complex, and they depend on both the intrinsic neuronal characteristics and stimulation parameters. These parameters include proximity of the implanted electrode to the target region, and the stimulation amplitude, frequency and pulse width [26]. A modeling study suggests that most of the cells within ~ 2 mm around the electrode will be excited at the stimulus frequency, whereas those stimulated at a subthreshold level will be inhibited [27]. A previous study showed that the neural architecture also plays a role in determining the result of stimulation. Myelinated axons have the lowest activation thresholds, while unmyelinated axons, dendrites, and cell bodies have a higher threshold [28]. In addition, neurochemical mechanisms, genes, and protein expression can also impact the efficacy of DBS [29].

Although focal-onset seizures such as TLE originate from specific brain regions, they often propagate along distinct neural pathways (Fig. 1) [10, 22]. Knowledge

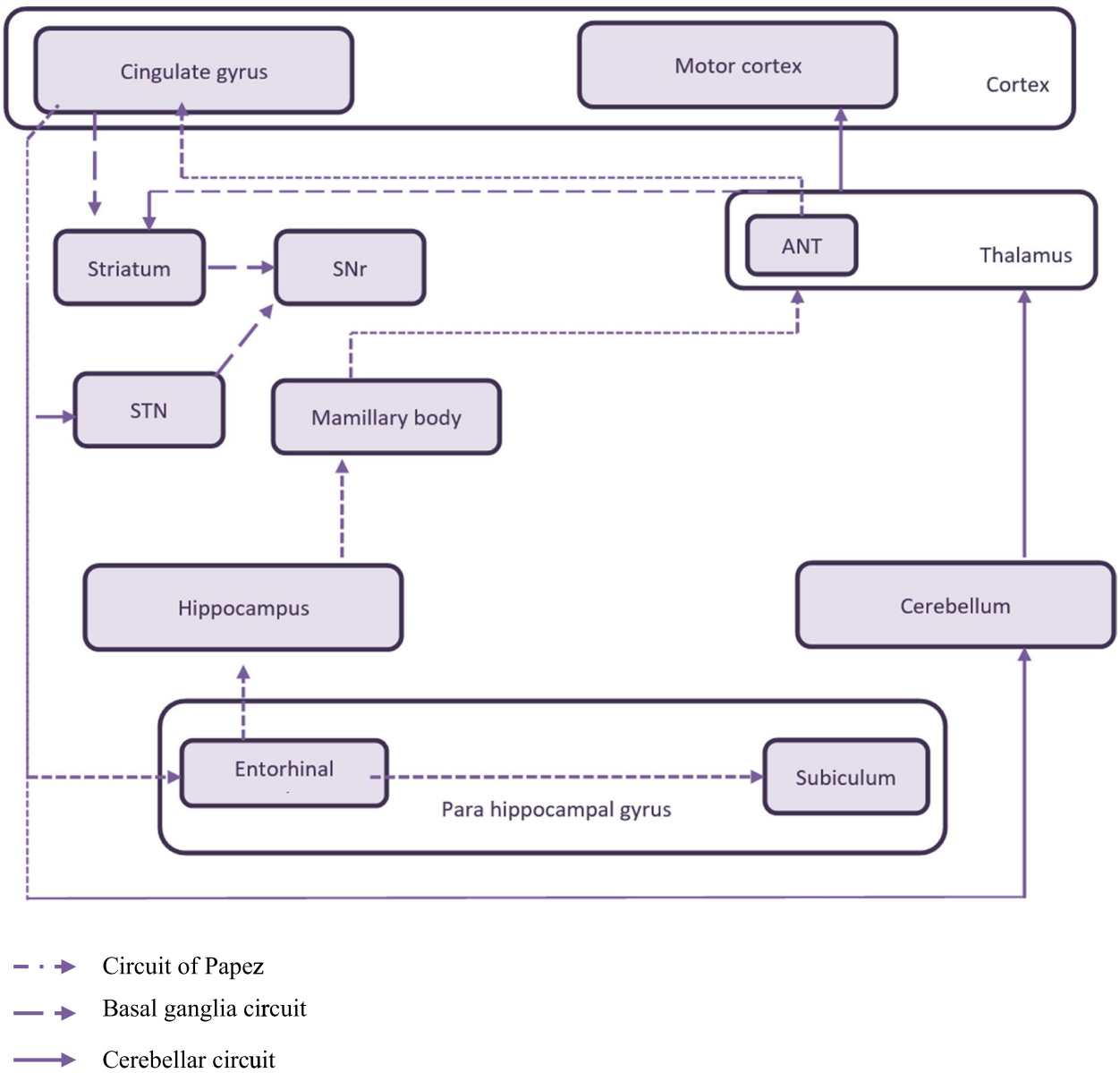

Fig. 1 Anatomical targets for neurostimulation and associated neural circuitry. SNr, substantia nigra pars reticularis; ANT, anterior thalamic nucleus; STN, sub thalamic nucleus

on these pathways, combined with lesioning studies in animal models, can provide insights into the targets for neuromodulation. Furthermore, as the cortical and subcortical brain regions along these circuits are functionally and anatomically connected, activity in one region would ultimately affect the activity in others. For example, disruption of the network at the level of the thalamus has been found to alter seizure propagation in frontal lobe and temporal lobe epilepsy [23, 24]. Additionally, a clinical trial has shown that stimulating the cerebellar dentate nucleus can inhibit seizure generalization. Therefore, this occurs as an indirect inhibition of the dentato-thalamo-cortical pathway [25]. Neuromodulation of the substantia nigra pars reticulata (SNr) via stimulation of the subthalamic nucleus (STN) has also been used in the treatment of epilepsy [5, 26]. High-frequency stimulation of the STN has been shown to be inhibitory for SNr by reducing the excitatory input from the STN to SNr [27, 28]. It has been suggested that there is an indirect pathway between the mesial temporal lobe and the STN despite

the lack of direct connection between the two structures [29]. The STN may also be responsible for seizure propagation through the motor cortex, resulting in generalization [30].

Anterior thalamic nucleus The efficacy of DBS was found to vary with the location of seizure foci [31]. In a longitudinal study where the anterior nucleus of the thalamus was stimulated among subjects with epilepsy, those with seizure focus in the temporal lobe showed greater median seizure reduction (44.2%) as compared to a 21.8% reduction in subjects receiving control treatment. However, the subjects with seizure focus in the frontal, parietal, or occipital region did not demonstrate significant differences in seizure reduction after stimulation compared to the control group [31].

Hippocampal formation For the purpose of this review, hippocampal formation refers to the dentate gyrus, hippocampus proper (i.e., Cornu Ammonis), and the subicular cortex. In most studies, hippocampal stimulation had encouraging results, with over 50% of the participants becoming seizure free [32–34]. However, TLE patients with HS had less favorable results than those without HS [35]. The reason may be that the response to stimulation is dependent on intact local neuronal networks, and therefore, the gliosis in HS patients impedes neuromodulation [36]. Paradoxically, some studies reported better results among patients with HS compared to those with normal MRI findings [33, 34]. Furthermore, reports on the microlesional effects caused by electrode implantation also show contradictory results. While some studies report absent or insignificant lesions [36, 37], other studies attribute the favorable results to the microlesions caused by electrode implantation [34].

Cerebellum There are limited studies assessing the use of cerebellar DBS in the treatment of epilepsy, particularly TLE due to the small sample size. One study showed that stimulation of the cerebellar dentate nucleus attenuated ictal as well as interictal seizure activity [25].

Basal ganglia Chkhenkeli et al. demonstrated that the unilateral low-frequency stimulation of the caudate head not only suppresses epileptic discharges bilaterally, but also reduces inter-ictal epileptic discharges on the ipsilateral side [25]. This stimulation also suppresses seizure generalization. Similarly, a case report showed that STN-DBS induced a 50% reduction in the seizures in a patient with TLE [28].

Safety and tolerability

Adverse effects of DBS are often a result of surgical complications, with electrode migration, surgical site infections, skin corrosion at the site of electrode placement, cerebral hemorrhages and cerebral edema being the most common adverse effects [31, 35, 38]. Apart from these, stimulation region-specific effects have also been noted. For example, stimulation of limbic structures has been found to affect both memory and emotion [33, 34, 39]; STN stimulation is associated with dyskinesia [28]; and cerebellar stimulation is linked to ataxia and dysmetria [25, 37]. Neuropsychological testing showed no marked changes in cognition, mood, or memory [31, 38].

TDCS

TDCS is a noninvasive neural electro-stimulation technique that delivers a low electric current via electrodes on the scalp to produce either negative (cathodal) or positive (anodal) stimulation. The setup consists of a stimulating electrode/active electrode and a return electrode attached to the scalp. The exact electrode position depends on the area of interest for stimulation. The electrodes are then connected to an external stimulator [40]. TDCS has been used in the treatment of depression [41], fibromyalgia [42], and epilepsy[43].

Mechanism of action

TDCS uses a low-intensity current (1–2 mA) that alters cortical excitability in one of two ways, cathodal or anodal stimulation. Cathodal stimulation causes hyperpolarization and thereby neural inhibition, whereas anodal stimulation excites the neurons through depolarization (Fig. 2) [44]. The excitation/inhibition imbalance seen in epilepsy can hence be attenuated by this application. Treatment of epilepsy focuses on cathodal stimulation. TDCS works at a cellular and synaptic level [45] where changes in protein synthesis, intracellular cyclic-AMP [46] and calcium levels [47] are observed. The effects have been found to persist even after cessation of the stimulus [48], which is of significance for determining the stimulation protocol. The "Hebbian" nature of this stimulation is associated with long-term potentiation and depression [49].

A recent review looking at the use of TDCS in epilepsy reported promising results, with 67% reduction of seizures and 83% reduction of inter-ictal epileptiform activity. The review included 65 participants across six studies, but did not specify those with TLE, making it hard to assess the efficacy of TDCS on TLE [50]. Research focusing on TDCS in TLE reported seizure freedom (50% seizure reduction) in 10 (83.3%) patients with TLE, while other 6 patients became

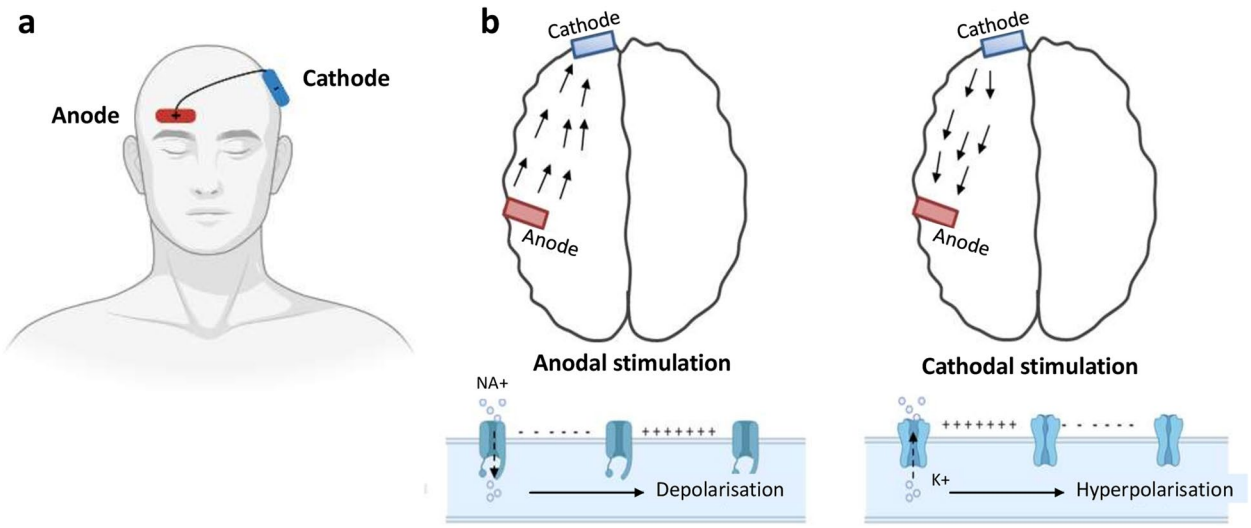

Fig. 2 **a** Electrode position for cathodal stimulation. The cathode is located over the affected temporal lobe and the anode is placed over the contralateral supraorbital area. **b** Effects of anodal and cathodal stimulation on membrane polarization. Created with BioRender.com

seizure free 1 month after stimulation and 2 patients were considered to be non-responders [51]. Another study reported that only 42.14% of patients with drug-resistant TLE showed reduced seizure frequency, but the stimulation had a sustained effect, as one patient receiving a 2-day stimulation had reduced seizure frequency for four months [52]. In another study, there was no initial significant seizure reduction after stimulation in the active group vs the sham group. However, after two months of follow-up, there was a 48% reduction in the mean seizure frequency in the active group and a significant reduction in cortical excitability [53].

The different results may be explained by the different stimulation protocols and continued use of antiepileptic drugs during treatment. It has been found that stimulation parameters such as intensity, duration and interval can greatly affect the efficacy of TDCS. Prolonged periods of high-intensity stimulation, for example, can result in stimulation at greater depth, subsequently leading to off-target effects [52, 54]. Therefore, a major goal of stimulation is to achieve maximum efficacy with minimal unwanted side effects. One study suggested that application of cathodal TDCS for 18 min with a 20-min interval after the first 9 min (9–20–9 protocol) will increase the inhibitory effects [52, 54]. Furthermore, repeated stimulation has also been shown to have prolonged inhibitory effects by affecting neuroplasticity [50, 51, 54].

Safety and tolerability

TDCS has been found to have minimal or no side effects. However, in some instances, high-intensity stimulation is associated with pain at the site of stimulation [55].

VNS

VNS includes manual or electrical stimulation of the vagus nerve for therapeutic purposes. The setup for VNS includes a surface pulse generator placed beneath the left clavicle and a stimulator on the cervical segment of the vagus. Early evidence of application of VNS for seizure regulation was first made in the 17th century, when manual massage of the carotid artery was found to suppress seizures [56]. This shed a light for therapeutic application of VNS in epilepsy and paved the way for later research. Electric VNS was conducted in animal studies and demonstrated anticonvulsant effects [57]. This technology was then approved for the treatment of drug-resistant epilepsy [58].

VNS can be applied on either the left or the right vagus nerve, although the right is not preferred as it is often associated with bradycardia and elevated blood glucose [59–61]. The left cervical VNS is approved for the treatment of drug-resistant epilepsy and depression, while the right cervical VNS has been studied for the treatment of heart failure in clinical trials [62]. The output current to the stimulator is regulated by the pulse generator according to the patient's tolerance, and a magnet may also be provided to patients to allow immediate cessation of stimulation in case of adverse events.

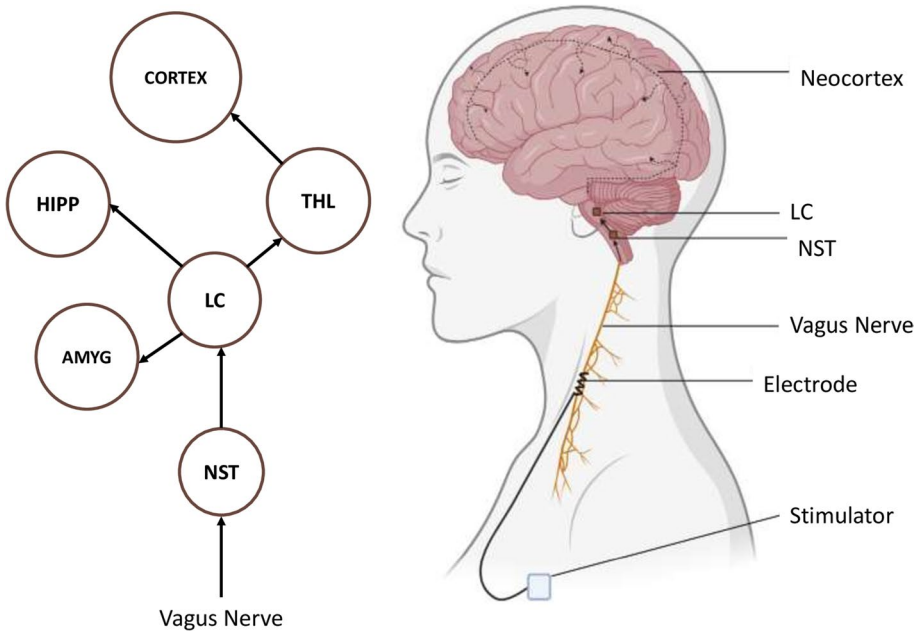

Fig. 3 Illustration of electrode placement in the neck accompanied with implanted stimulator, and the efferent vagus nerve pathway**.** The nucleus of the solitary tract (NTS) receives information from afferent fibers in the vagus and sends excitatory fibers, mostly glutamatergic, to the locus coeruleus (LC). This in turn sends noradrenergic projections to the amygdala (AMYG), thalamus (THL) and hippocampus (HIPP), and finally the cortex receives thalamic inputs. Created with BioRender.com

Mechanism of action

The vagus nerve is the mixed cranial nerve that consists of both sensory/afferent fibers and motor/efferent fibers. The sensory fibers originate from the heart, aorta, lungs, and gastrointestinal tract [63] and comprise 80% of the nerve fiber, while the efferent fibers form part of the autonomic nervous system (parasympathetic). The afferent fibers project to the nucleus of the solitary tract (NST) which has widespread projections to several areas in the forebrain and the brainstem, and is the target for therapeutic application of VNS. The NST sends excitatory outputs to the nucleus paragigantocellularis, which in turn sends excitatory outputs to the locus coeruleus (LC). The LC then sends adrenergic inputs to the hippocampus and amygdala (Fig. 3) [64, 65]. The mechanism of VNS-induced seizure reduction involves the inhibition of limbic projections from the NST to the LC, as the LC has been identified as an area of epileptogenesis and seizure generalization [65]. This has been demonstrated when lesioning the LC in rats blocked the anticonvulsant effects of VNS [66].

Research on VNS has reported long-lasting seizure reduction in TLE patients with both unilateral [15] and bilateral [67, 68] seizure foci. The effect of VNS on seizure reduction continued even after the stimulation was stopped. Repeated stimulation may increase the efficacy of the treatment [69]. García-Navarrete et al. reported a 63% seizure reduction in 80% of their participants [15]. These results are comparable to other studies, which reported a 60% seizure reduction in five patients presenting with bi-temporal TLE, and an average of 50% seizure reduction one year after stimulation [67]. Another study reported a sustained effect and a 42% seizure reduction at 18 months post stimulation [68].

Reduction in the inter-ictal epileptiform discharge has been found to be a major predictor for good prognostic outcome. This was confirmed by Janszky et al. [70], who found that the absence of bilateral inter-ictal epileptiform discharge was associated with favorable outcomes. However, one study reported that compared to the patients with bilateral inter-ictal discharges, the only one patient with no inter-ictal discharges displayed no difference in seizure reduction [67].

Safety and tolerability

A longitudinal retrospective study assessing the complications and safety of VNS showed an overall complication rate of 12.4% [71]. These complications include surgical complications such as hematomas, surgical site infection and migration of the device as well as complications brought about by vagus nerve injury such as vocal cord palsy and subsequent hoarseness of voice [15, 67, 68, 70]. As the vagus nerve has autonomic functions,

changes in its properties as a result of stimulation have autonomic impacts. These impacts are thought to manifest in the heart as bradycardia and hemodynamic instability [59, 71]. In contrast, recent studies have found no significant changes in heart rate variability and blood pressure in patients with VNS [72]. In a previous study, severe side effects were seen in some patients with TLE, which ultimately led to removal of the implant [15]. The side effects included infection in two patients, painful swallowing in one patient, and exacerbation of a preexisting behavioral problem in one patient, who displayed severe aggression [15].

TMS

TMS is an intervention that uses external magnetic fields to modulate neural behavior. The magnetized coil is placed over the desired target and produces a magnetic field of about 2 T. To localize the epileptogenic focus, EEG monitoring and magnetic resonance imaging (MRI) are used for accurate placement of the coil. TMS is used in the management of several conditions such as stroke, depression, and amyotrophic lateral sclerosis [73–76]. Having an ability to alter cortical excitability, TMS has also been applied in the treatment of epilepsy [77]. Apart from medical therapy, TMS is also used in neurocircuit research based on its ability to delineate specific targets [78]. In conclusion, TMS is a non-invasive and relatively pain-free therapy, and produces sustained effects after repeated stimulation [79], which make it a preferred method for neuromodulation.

Mechanism of action

A TMS device consists of copper coils that produce a magnetic pulse, which in turn induces an electrical current, causing depolarization in nearby axons. Reithler et al. hypothesize that low-frequency stimulation results in inhibition of the targeted neural population via prolonged synaptic depression/ long-term depression [80]. This has been demonstrated in animal studies in which TMS caused initial excitation followed by a delayed inhibition [81]. The exact mechanisms underlying the effects of TMS are not clear; however, the effects have been shown to vary based on the strength of stimulation and even between types of neurons stimulated. Evidence shows that repeated TMS induces plasticity of specific synapses on principal neurons, while 10-Hz stimulation causes dendritic but not somatic inhibition [82], although small dendritic spines close to the soma of pyramidal neurons may not have the same response [82, 83]. This feature is specifically of interest in TLE as stimulation of the cortex could facilitate plasticity along the thalamo-cortical projections. The range of effect of the device can be altered based on the frequency, intensity, and duration of stimulation as well as positioning and size of the coil used. Although local stimulation occurs up to 2 cm deep, TMS can also affect distant areas [80].

We found little evidence on the efficacy of TMS on TLE [84–86]. Although TMS showed minimal therapeutic effects on achieving seizure freedom, one study further compared effects at different stimulation intensities, and found that high-intensity (90% resting motor threshold) stimulation decreased the frequency of seizures at a greater extent than low-frequency (20% resting motor threshold) stimulation (79.8% vs 2.3% reduction) [84]. The frequency used was 0.5 Hz, which was consistent with other studies that observed cortical inhibition [14, 86, 87]. Among the responsive patients, a trend was observed with greater seizure reduction in patients with neocortical than with mesial temporal foci [85, 88].

The poor response of TLE to TMS could possibly be explained by the depth of seizure foci in mesial TLE. The effect of TMS deteriorates by the square of the distance; therefore, direct effects on subcortical structures are minimal [89]. Direct stimulation of the correct epileptic focus is found to be critical for improving response to TMS [14, 43]; however, based on the anatomical location of the epileptic foci in TLE, localization may be difficult. Furthermore, TMS has been shown to work for patients whose epileptic foci are located on the cortical convexity [85], though it has also been noted that TMS can exert effects on distant targets along specific neural networks [90, 91]. The latter has been demonstrated by the finding that stimulation of the primary sensory-motor cortex is associated with activation of deeper structures such as the putamen and thalamus [90]. This effect is promising as it allows for further research into indirect neuromodulation in TLE.

Safety and tolerability

The most common side effects of TMS are local pain during stimulation (such as headache) occurring in less than 2% of participants, often with higher intensity of stimulations [84, 85, 92].

Discussion

In this review, we discuss the clinical application of neuromodulation in the treatment of TLE. Neuromodulation has promising applications in TLE, but produces variable results. In addition to therapeutic outcomes, differences in application techniques (invasive *versus* noninvasive) also play a role in selecting the therapy. As these therapies vary widely in their application, it is not feasible to

propose the use of one over the other. However, to make general recommendations on the use of neuromodulation in clinical treatment of TLE, one must accept the compromise between potential benefits and harms. Such decisions should be made on an individual basis after discussion with the patient's attending physician. In this section, we will provide suggestions on how to improve clinical trials in the future based on deficits observed.

One of the major limitations of neuromodulation research is the small number of study participants, particularly patients with TLE. Of the potential neuromodulatory techniques, only a few have been studied in randomized and double-blind trial settings and the sample size of TLE patients in the under-going trials is small. Given the limited research currently available, more clinical trials are required to provide evidence on the efficacy and safety of neuromodulation in the treatment of TLE. A large sample size may reduce the risk of bias and produce evidence for introduction of neuromodulation in the clinical management of TLE. However, as patient recruitment is difficult, smaller trials in multiple centers would increase the available evidence and allow for more concise findings.

Another limitation is the lack of necessary long-term follow-up trials. A long-term follow-up may provide insight on the persistence of response to stimulation, including the response in the wash-out period, and possible side effects that may arise from chronic stimulation. In addition to this, longer follow up allows for clear interpretation of stimulation parameters. For example, a study assessing the effects of hippocampal electric stimulation in TLE showed that seizures continued to decrease by 25% in two patients during a three-month period after cessation of stimulation [35]. The micro-lesions during implantation may have been missed if there is no related assessment after DBS implantation prior to initiation of stimulation. Similarly, the presence of HS could affect the response to therapy. A study using DBS noted that a one-month follow-up period was insufficient for patients with HS to show a response [39]. Therefore, introducing a washout period in the protocol or using alternative study designs such as a parallel study design may allow for assessment of any carryover effects.

In addition, another limitation is the variations of outcome measures reported. Almost all the reviewed papers have reported seizure frequency as the primary outcome measure, a few studies reported on the inter-ictal discharges, and even fewer reported neuropsychological tests and quality of life as secondary outcomes. TLE is often associated with cognitive impairment by virtue of the area of the brain affected; moreover, the associated inter-ictal activity further increases cognitive impairments [9]. It is therefore important that inter-ictal activity is measured and neuropsychological tests performed as part of the treatment protocols.

Future direction

There are exciting tools that allow modulation of neuronal populations with extraordinary specificity, which may pave the way for improved TLE interventions. Among these are targeted gene therapies such as optogenetics and chemo-genetics. Optogenetics uses light-sensitive proteins called opsins in excitatory channels or inhibitory channels to modulate the activity of neurons, by controlling opsins using light of specific wavelengths [93]. Chemo-genetics on the other hand uses designer receptors, which are only activated by designer drugs for specially designed ligands [94]. Given their selective expression, optogenetics and chemo-genetics can modulate neuronal populations with incredible specificity and remarkable temporal precision. Additionally, they allow direct modulation of the excitatory/inhibitory imbalance in epilepsy as they act to excite or inhibit circuits based on the experimental design. Such specificity minimizes off-target effects and consequently provides a tailored treatment with less side effects.

Chemo-genetics and optogenetics have resulted in significant seizure reduction in both acute and chronic models including animal models of TLE [95, 96]. In addition to this, ex vivo inhibition of epileptic discharges has also been demonstrated [97]. Apart from the potential therapeutic application, these tools can also advance our understanding of the neural circuitry in epilepsy [93], thus providing potential targets for indirect neuromodulation. There have been several papers discussing the use of chemo-genetics and optogenetics in preclinical animal models; however, there are still some concerns before translation to clinical use.

A major concern for their translation is patients' safety. Although viral vectors have been used in clinical trials without major side effects [98], there are still concerns on the practicality of the tool in humans. One such concern is targeting desired neural population for the expression of opsins. Additionally, there is the concern of long-term effects of gene therapy. A specific concern with chemo-genetics is the pharmacodynamic/pharmacokinetic effects of the ligand clozapine-N-oxide (CNO). CNO is readily metabolized into clozapine [99] which can then attach to several other receptors. This effect could be overcome by using alternative ligands such as olanzapine, which is already approved for human use and has minimal side effects. In addition to this, as more recent developments in chemo-genetics, pharmacologically selective actuator and effector modules (PSAM/PSEM) use modified endogenous receptors and specially designed ligands for neural modulation [94].

In the case of optogenetics, the mode of light delivery is a unique challenge, including the safety of implantation and adequacy of stimulation. The implantation of the light probe could potentially be done in similar ways as electrodes in electric stimulation, provided that the probes are robust. The adequacy of light stimulation is, however, a more challenging issue, as the wavelengths commonly used are easily absorbed by the brain tissue [100]. To mitigate this problem, different wavelengths of light may be used, therefore opsins that are sensitive to these wavelengths must be developed. Research on red-light sensitive opsins [101, 102] has been done with some success, as red light is absorbed less by the brain tissue and thus is able to penetrate to subcortical structures. For the issue of viral delivery and expression, adeno-associated virus has been safely used in several phase I and II clinical trials [98]. Another bottleneck in clinical translation from rodent models is the difference in brain size. A human brain is ∼1000 times bigger than that of a mouse, which necessitates research on bigger animals. Research using optogenetics in Parkinsonian monkey models has shown positive outcomes and proves that they may be a suitable transition from rodents to humans [103]. This difference in size brings up challenges in viral volume injection, transduction specificity, as well as illumination coverage. As the probe must be thin enough to avoid structural damage and the light intensity be low enough to avoid phototoxicity, better probe designs may be required. For this, Tønnesen and Kokaia have designed an optrode with multiple fiber bundles that could cover larger areas [104].

Conclusions

The progress that has been made is very encouraging for the use of modulatory therapies to modify network dysfunction in epilepsy. However, due to the small sample size, varied inclusion criteria (bilateral vs unilateral epileptic foci, the presence of sclerosis) and the lack of long-term follow-up of the participants, clear conclusions cannot be made as to the best practice. In addition, most studies did not report the inter-ictal epileptiform results. Technique improvement and patient safety are key to translation of preclinical experiments. Considering the promising but variable results, more well-designed studies are needed to evaluate the efficacy of these treatments and compare them with other neuromodulatory approaches as well as existing surgical and medical treatments.

Abbreviations

DBS: Deep brain stimulation; EEG: Electroencephalography; GABA: Gamma-amino butyric acid; HS: Hippocampal sclerosis; LC: Locus coeruleus; MRI: Magnetic resonance imaging; NST: Nucleus of the solitary tract; SNr: Substantia nigra pars reticularis; STN: Sub-thalamic nucleus; TLE: Temporal lobe epilepsy; TMS: Transcranial magnetic stimulation; VNS: Vagus nerve stimulation; PSAM: Pharmacologically selective actuator module; PSEM: Pharmacologically selective effector module.

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Authors' contributions

AAE searched for and reviewed the existing studies. AT also reviewed the final manuscript and made valuable suggestions and was a major contributor to the writing of the manuscript. All authors read and approved the final manuscript.

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