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SUPPLEMENT ARTICLE

Clinically indicated electrical stimulation strategies to treat patients with medically refractory epilepsy

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Summary

Focal epilepsies represent approximately half of all diagnoses, and more than one-third of these patients are refractory to pharmacologic treatment. Although resection can result in seizure freedom, many patients do not meet surgical criteria, as seizures may be multifocal in origin or have a focus in an eloquent region of the brain. For these individuals, several U.S. Food and Drug Administration (FDA)–approved electrical stimulation paradigms serve as alternative options, including vagus nerve stimulation, responsive neurostimulation, and stimulation of the anterior nucleus of the thalamus. All of these are safe, flexible, and lead to progressive seizure control over time when used as an adjunctive therapy to antiepileptic drugs. Focal epilepsies frequently involve significant comorbidities such as cognitive decline. Similar to antiepilepsy medications and surgical resection, current stimulation targets and parameters have yet to address cognitive impairments directly, with patients reporting persistent comorbidities associated with focal epilepsy despite a significant reduction in the number of their seizures. Although low-frequency theta oscillations of the septohippocampal network are critical for modulating cellular activity and, in turn, cognitive processing, the coordination of neural excitability is also imperative for preventing seizures. In this review, we summarize current FDA-approved electrical stimulation paradigms and propose that theta oscillations of the medial septal nucleus represent a novel neuromodulation target for concurrent seizure reduction and cognitive improvement in epilepsy. Ultimately, further advancements in clinical neurostimulation strategies will allow for the efficient treatment of both seizures and comorbidities, thereby improving overall quality of life for patients with epilepsy.

KEY WORDS: **Epilepsy, Electrical stimulation, Deep brain stimulation, Theta oscillations, Medial septal nucleus.**

Epilepsy, as defined by the presence of spontaneous recurrent seizures, has an estimated lifetime prevalence of 1–5% globally, making it the fourth most common neurologic disorder.[1–5] Within the United States alone, there are approximately 3 million adults and 470,000 children currently diagnosed with epilepsy.[6] As of 2017, epilepsy syndromes are operationally classified as focal (partial), generalized, or unknown onset.[7] The origin of focal seizures can be subdivided by topographic location (i.e., subcortical, temporal, frontal, occipital, or parietal lobe epilepsy). Collectively, focal-onset epilepsies represent more than half of all diagnoses[8]; among these, temporal lobe epilepsy (TLE) is the most prevalent.

Pharmacoresistance is most common in focal epilepsies such as TLE.[8] In fact, ~40% of patients with TLE are refractory to medical intervention and have persistent seizures.[8,9]

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Key Points

- Electrical stimulation is indicated for patients with medically refractory epilepsy who do not qualify for surgical resection
- Vagus nerve stimulation, responsive neurostimulation, and stimulation of the anterior nucleus of the thalamus reduce seizures by 50–70%
- Theta stimulation of the medial septum represents a potential therapy to reduce seizures and improve cognition in temporal lobe epilepsy

Patients whose seizures cannot be controlled have higher rates of morbidity and mortality, including trauma, suicide, and sudden unexpected death in epilepsy.[10,11] For refractory patients, resection of the seizure focus is a potential treatment option. However, eligibility for resection depends on location of the seizure focus, including the surgeon's ability to identify and safely remove the epileptic tissue. Furthermore, of those patients receiving resective surgery, only 50–70% become seizure-free.[12,13] Therefore, there is a clear need to develop additional adjunctive therapies for the treatment of refractory epilepsy.

Over the last 50 years, neurostimulation has been established across multiple preclinical and clinical trials as a safe and reversible surgical option that can be combined with traditional medical interventions to significantly reduce seizures. Currently, there are 3 U.S. Food and Drug Administration (FDA)–approved neurostimulation paradigms: vagus nerve stimulation (VNS), responsive nerve stimulation (RNS), and deep brain stimulation (DBS). However, there is still room for optimization of neurostimulation for epilepsy, specifically in terms of improving seizure reduction and treating common comorbidities of epilepsy, such as cognitive dysfunction.[14] This review will address current FDA-approved neurostimulation treatment strategies. Furthermore, we will discuss evidence supporting the hypothesis that driving theta oscillations via stimulation of the medial septal nucleus (MSN) has the potential to both reduce seizures and improve cognitive outcome. Ultimately, the development of a range of tools, including neurostimulation, maximizes our ability to achieve seizure freedom and improve quality of life for patients with refractory epilepsy disorders.

Primary Treatment Strategies for Focal Epilepsies

Anti-epileptic drugs

The first line of treatment for epilepsy is administration of antiepileptic drugs (AEDs). There are multiple pharmacologic strategies targeting a range of ion channels and receptors, each with the goal of modulating the balance of synaptic excitation and inhibition.[15,16] Approximately 47% of patients achieve seizure freedom with one AED; however, if ineffective, adding a second drug (serially or in combination) yields only an additional 11% remission rate, and subsequent addition of drugs contributes less than a 3% improvement in efficacy.[9,17] Ultimately, only ~60% of patients respond to AEDs. Epilepsy is considered refractory or pharmacoresistant when administration of 2 AEDs, either serially or combined, fails to achieve seizure freedom after 2 years.[8,17,18] Patients experiencing years of seizures, and those who develop structural abnormalities, are 50% more likely to become refractory to medication. Refractory patients account for 80% of the total (direct plus indirect) cost of epilepsy in the United States, which is estimated to be over $15.5 billion annually.[19,20]

Pharmacoresistance is most common in focal epilepsies[8,21] and is frequently associated with cognitive decline. For example, approximately 70% of patients with TLE exhibit memory impairment.[14] Furthermore, unmanaged epilepsy can result in increased rates of morbidity/mortality and decreased quality of life, as patients may be legally unable to drive and socially unable to conduct normal vocational and recreational activities.[11,22,23] Even in cases of pharmacoresponsive epilepsy, the adverse side-effects of AEDs can impair quality of life, as drugs that reduce excitability and seizures are associated with exacerbation of cognitive and mood comorbidities.[24–27] Moreover, drug–drug interactions with other important medications, such as birth control,[28] can impair quality of life, even in the context of reduced seizures.[27] Over 80% of patients taking more than one AED report an average of 6–7 medication-related adverse effects,[26] leading to a 20% noncompliance rate.[29–31] Ultimately, noncompliance can result in uncontrolled seizures in patients who choose to discontinue AED use.

Resection

The only curative option for focal epilepsy is resection, which is effective in 50–70% cases, depending upon epilepsy type, focus, and patient age.[12,13] Among all epilepsies, surgical treatment is most commonly used for and efficacious in treating TLE. However, surgically eligible patients often wait more than 20 years for resection, during which time they continue to have seizures.[32,33] In addition, some patients, such as those with generalized or multifocal epilepsy, or those with an epileptic focus in a key language area, are ineligible for resection.[34] Even when surgery is curative, removal of temporal lobe tissue can have deleterious effects on cognitive function.[35–39] Therefore, too many patients taking AEDs for focal epilepsy, and particularly TLE, continue to experience uncontrollable seizures, persistent comorbidities, and drug-related side effects. This emphasizes a clear need for alternative therapies, such as neurostimulation, that can be applied in combination with AEDs to better reduce seizures and seizure-related comorbidities.

Neurostimulation to Treat Epilepsy

Neurostimulation involves the delivery of a stimulus (electrical or magnetic) to specific targets within the central or peripheral nervous system, which modulates a pathologic substrate to yield a therapeutic effect. The first neurostimulator was implanted in 1967 as an analgesic therapy.[40] Since then, stimulation of the central nervous system has been indicated for treatment of many conditions (Fig. 1), including neuropathic and ischemic pain (reviewed in[41]), motor disorders,[42–48] obsessive compulsive disorder,[49] Tourette syndrome,[50] depression,[51] obesity,[52,53] and medically refractory epilepsies.[54–56]

Neurostimulation is a safe, effective option for patients with intractable epilepsy who fail to meet surgical criteria. Current is delivered at a customizable frequency, amplitude, and pattern (i.e., continuous, cycled, or triggered), which can be tailored to the individual and subsequently discontinued if determined to be deleterious.[57,58] Three types of neurostimulation—VNS, RNS, and DBS of the anterior nucleus of the thalamus (ANT)—are FDA-approved for the treatment of medically refractory epilepsy.[54,59,60] In the following sections, we discuss preclinical and clinical evidence for the safety and efficacy of each of these paradigms, focusing primarily on the most recent reports from long-term studies. It is important to note that these still ongoing trials (over 7 years) are open-label, uncontrolled trials, and therefore there may be some limitation in our ability to interpret the data. For example, it would be difficult to assess the relative roles of continued medical management and potential placebo or lesion effects of the implantation on seizure control. However, these therapies have also been evaluated in short-term, randomized, and double-blinded pivotal studies.[56,61,62] Moreover, most of these patients did not respond, either actively or with placebo, to an average of 20 years of pharmacologic management. Critically, each of the FDA-approved neurostimulation therapies, whether independently or in conjunction with continued medical management, results in a significant reduction of seizures in the majority of patients.

Vagus nerve stimulation

Current developments of clinical targets for modulation have been, and continue to be, guided by preclinical animal research. As early as 1937, animal studies have indicated that stimulation of the vagus nerve has the potential to desynchronize electroencephalography (EEG) activity as a result of widespread cortical connections mediated by vagal afferents that terminate in the nucleus of the solitary tract.[63–66] Subsequently, studies in multiple models, ranging from rats induced with pentylenetetrazol (PTZ) and

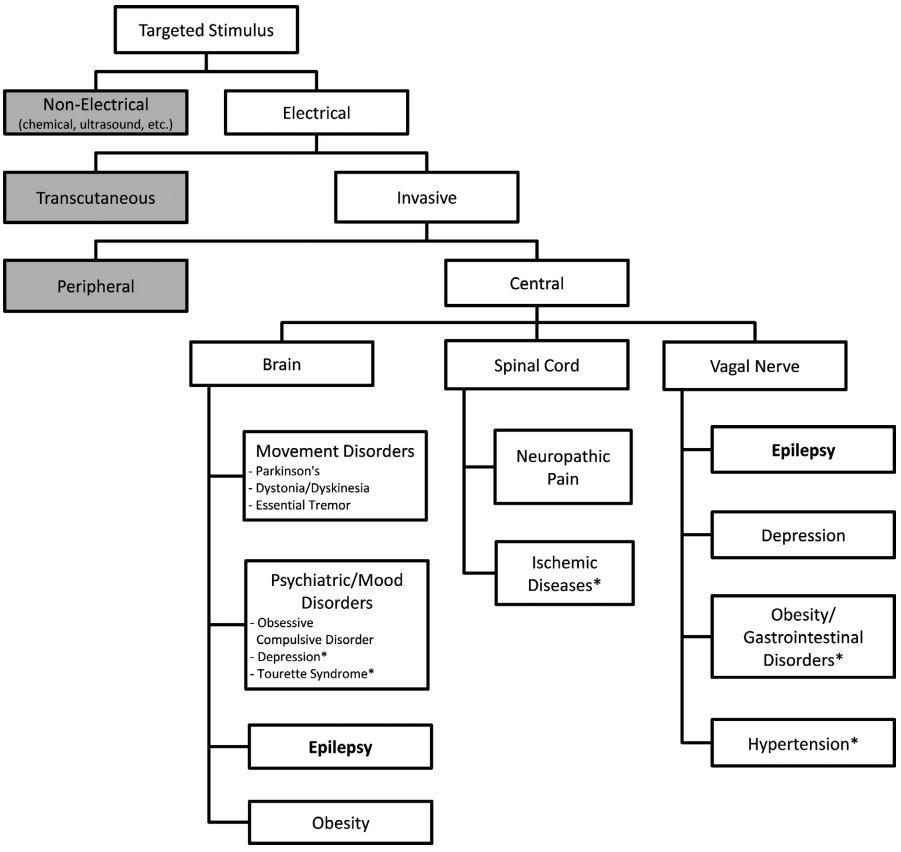

Figure 1.
Clinical applications of invasive, central neurostimulation.[41–56,170–173] Therapeutic neuromodulation is the targeted injection of an electrical, chemical, or other nonelectrical stimulus to a specific region. Neurostimulation at multiple central nervous system targets has been FDA-approved for a variety of clinical indications and is under consideration (*) for several others. *Epilepsia Open* © ILAE

maximal electroshock to nonhuman primates exhibiting spontaneous seizures, have demonstrated the safety and efficacy of VNS for preventing or interrupting ictal activity.[63,67,68]

Since the first human implantation in the late 1980s,[69] VNS has been approved as an adjunct therapy for medically refractory epilepsies in adults and children (>12 years), particularly when resection is contraindicated or fails to reduce seizures.[54,70] A programmable pulse generator is implanted subcutaneously and connected to the left vagus nerve via a tunneled bipolar stimulation lead.[61] Stimulation is delivered in an open-loop manner (continuous or cycled, e.g., 1 minute on, 5 minutes off) but can also be triggered by changes in cardiac rhythm[71] or with a handheld magnet.[72] Initial studies demonstrated that higher frequency (20–50 Hz) stimulation was more effective than low frequency (1–2 Hz) stimulation for seizure reduction.[61,73] In longitudinal trials (Table 1), VNS yields a median responder rate of 22.1–44.4% after 1 year, 38.1–54.4% after 2 years,[74–76] and 43.8–58.9% by the end of year 5.[74,75] In addition, 3.3% of the patients were seizure-free after 2 years, and 5.5% achieved seizure freedom after 5 years.[75] A common criticism of the clinical trials for neurostimulation, however, is that the effects of stimulation cannot be evaluated independently of AEDs because patients remain on pharmacotherapy. For example, VNS patients, on average, had an increase in their AED regimen 2 and 5 years following implantation.[74] However, there was no difference in efficacy between VNS responders who remained on a stable course of AEDs throughout the 5-year period and those whose medication regimen was decreased during the trial.[74]

Adverse effects associated with VNS implantation most commonly include implant site infection (7%), vocal cord paresis (5.6%), and device-related complications such as VNS lead fracture and malfunction (16.8%).[77] Very rarely, stimulation of the left vagus nerve can be associated with bradycardia and/or asystole, although this has been reported mostly intraoperatively, and instances of late-onset bradycardia or arrhythmias are infrequent.[77–80] Although outcomes can vary, VNS remains an option for patients with epilepsy, and the only neuromostimulation therapy approved for children that can reduce seizure frequency and severity without requiring cranial surgery.

Responsive neurostimulation

Several preclinical studies have investigated the efficacy of closed-loop stimulation, aiming to better predict ictogenesis while minimizing stimulation exposure. For example, Wagenaar and colleagues designed an in vitro closed-loop feedback system in which the firing rate of cultured neurons was monitored in real-time and used to optimize stimulation parameters to efficiently suppress synchronized bursts.[81] In an in vivo model of pilocarpine-induced epilepsy, seizures were predicted based on pre-ictal synchronization, and the centromedian nucleus of the thalamus was stimulated at high frequency to prevent seizures.[82] Predictive stimulation resulted in significant seizure reduction in 33% of rats, compared to only 17% of rats receiving open-loop (preprogrammed) stimulation. Furthermore, stimulation success was correlated with desynchronization of brain activity.[82] In a separate study, Liang and colleagues aimed to develop a highly accurate seizure prediction algorithm in Long-Evans rats exhibiting both spontaneous and PTZ exposure–associated spike-wave-discharges.[83] Frontal lobe seizure activity was accurately predicted in approximately 92% of instances. Furthermore, 800 Hz stimulation of the zona incerta occurred within 0.6 seconds of detection and successfully interrupted ictal activity.[83] Collectively, these experimental studies provide evidence in support of the clinical viability for closed-loop (responsive) stimulation in epilepsy.

The NeuroPace RNS stimulator is an FDA-approved, closed-loop neurostimulation device for patients with intractable epilepsy associated with one or 2 seizure foci.[55,60,62,84,85] The RNS device continuously monitors EEG, and when an abnormal pattern is identified (according to criteria that are programmed and can be modified by the physician), high-frequency stimulation pulses are delivered immediately to the seizure focus.[62] This device is fully programmable and is connected to 2 electrodes (depth or

Table 1. Longitudinal efficacy of neurostimulation therapies.

	Year 1				Year 2				Year 5/6			
	n	Median seizure reduction	Responder rate	Seizure freedom	n	Median seizure reduction	Responder rate	Seizure freedom	N	Median seizure reduction	Responder rate	Seizure freedom
VNS	90	NR	44.4%	0%	87	NR	58.9%	3.3%	90	55.9%	64.4%	5.5%
RNS	197	44%	43%	NR	174	53%	54%	9%	mTLE: 106	70%	66%	20.8%
									Neocortical: 90	55%	77%	26%
DBS	105	41%	43%	NR	82	56%	NR	NR	83	69%	68%	16%

VNS efficacy was evaluated 1, 2, and 5 years into the open-label period.[75] RNS efficacy was reported at 1 and 2 years postimplantation.[55] Specific efficacy in mTLE was reported in year 6, and seizure freedom rate was based on the previous 6 months.[84] Year 6 efficacy in neocortical epilepsy was based on the previous 3 months.[85] DBS efficacy was evaluated in years 1, 2, and 5 of the open label-period, and seizure freedom rates were based on the previous 6 months.[59]

subdural), with placement depending on an estimated seizure focus based on prior intracranial monitoring. Each electrode has 4 contacts, which can each be used for both recording and stimulation.[62] During the open-label period, RNS resulted in median seizure reductions of 44% and 53% at the end of the first and second years, respectively.[62] After 6 years of evaluation, 84% of patients had some seizure reduction, of which 60% were responders (≥50% reduction) and 16% were seizure-free.[60] Of interest, follow-up studies reported that patients with focal epilepsy responded differently depending on seizure focus (Table 1). TLE patients treated with RNS had a median seizure reduction of 70%, and the responder rate was 66%.[84] In patients with neocortical epilepsy, the median reduction was 55%, and the responder rate was 77%.[85]

Adverse side effects associated with RNS included implant site infections (11.7%), resulting in 9 explants and 7 (6.3%) device lead replacements, and a 2.7% risk of intracranial hemorrhage.[84] Patient-reported adverse events related to depression and memory impairment in the RNS trial were 1.8% and 6.3%, respectively.[84]

Deep brain stimulation

Although DBS has been investigated in various brain structures in preclinical models of epilepsy, the ANT has drawn significant interest, as it is reciprocally connected with the hippocampus and limbic structures and has been hypothesized to drive synchronization during ictal activity.[86–88] Accordingly, lesions to the ventral anterior thalamus significantly reduced ictal frequency in felines experiencing acute epilepsy (tungstic acid gel) and also in a nonhuman primate model of chronic epilepsy (aluminum hydroxide gel).[89] DBS paradigms, such as high-frequency stimulation of the ANT, have been shown to increase seizure threshold in rats with acute PTZ-induced seizures.[90] Similarly, bilateral stimulation of the ANT significantly delayed the development of acute pilocarpine-induced seizures and status epilepticus, with both high- and low-frequency stimulation (130 vs. 20 Hz) exhibiting similar inhibitory effects.[91–93] Separate studies have also demonstrated reduced ictal activity resulting from ANT stimulation in both kainic acid[94] and kindling rodent models[95] of chronic TLE. Although these animal studies represent only a small subset of the preclinical evidence in support of DBS, they provided specific support to drive the translation of current clinically indicated stimulation paradigms.

DBS uses an open-loop stimulator[56,59] connected to depth electrodes implanted in the bilateral ANT. The stimulator is programmed to deliver continuous or cycled, high-frequency stimulation rather than responding to ictal activity.[56] One year after implantation, patients experienced median seizure reductions of 44% for temporal lobe seizures and 53% for frontal lobe seizures.[59] By 5 years, median reductions improved to 76% in temporal lobe seizures and 59% for frontal lobe seizures. It is important to note that after 5 years, 16% of patients had demonstrated seizure freedom in the previous 6 months (Table 1).[59] In a separate study of 29 patients followed for 11 years, DBS of the ANT resulted in a median 70% reduction in total seizures.[96]

Similarly to RNS, the DBS trial reported implant site infections in 10% of patients; however, the authors also reported incorrect lead position in 8.2% of the cases (possibly due to variability between frame and frameless implantation procedures).[97] In addition, a 7-year mood and memory outcome study in the DBS trial revealed that 14.8% and 13% of the active stimulation group reported an adverse event related to depression and memory, respectively.[7] Critically, many patients in this study had a history of depression and cognitive impairment prior to implantation, and investigators found no significant difference between baseline and follow-up measures of neuropsychological scores and neurobehavioral function.[98]

Cognitive Dysfunction in Focal Epilepsies

The association between focal epilepsies and cognitive impairments, although not well-characterized, is multifactorial and not limited to a specific focal seizure classification (focal seizures with awareness vs. focal seizures with impaired awareness, i.e., simple vs. complex).[7,99,100] Factors contributing to cognitive deficits can include age at seizure onset,[101] duration of intractable seizures,[102] number/intensity of seizures,[103] lateralization of seizures,[104] abnormal electrical activity,[105] hippocampal sclerosis,[106,107] impairments resulting from resection of ictal foci,[39] and the side effects of AEDs.[25,26,108] Patients with TLE exhibit impairments in multiple memory domains, including spatial working memory[104,107,109] and subsets of declarative memory, such as episodic memory.[110,111] For example, in a virtual reality spatial task, patients were instructed to identify the location of spatially distributed reward boxes that were dispersed among empty boxes.[109] Through 10 successive trials, patients with TLE made more errors and traveled longer distances (i.e., less efficient) to locate the reward boxes, as compared to controls.[109] In addition, visuospatial working memory was impaired in TLE patients tested on a nonvirtual task called the 9-box maze.[107] Notably, deficits were significantly correlated with medial temporal lobe damage, including hippocampal sclerosis.[107] In sum, these data suggest a direct relationship between TLE and significant cognitive disability.

A critical shortcoming of all current treatment paradigms for focal seizures, including AEDs, resection, and neurostimulation, is that treatment efficacy is defined primarily in terms of seizure control in the absence of significant side effects; none of these strategies directly target comorbidities such as cognitive decline.[24–26,39] AEDs are associated with exacerbation of cognitive and mood comorbidities,[24–27] and resection of temporal lobe tissue can have lasting effects on

cognitive function, such as decline in verbal or visuospatial memory,[35–39] particularly depending on the size and location of the lesion. Furthermore, although each of the 3 neurostimulation paradigms result in significant seizure control, only modest improvements in specific measures of learning and memory are apparent in a small fraction of patients. Others continue to report cognitive dysfunction and, in some cases, further decline. In a recent follow-up study in patients implanted with the RNS system, patients with neocortical seizures, but not those with temporal seizures, demonstrated improved performance on the Boston Naming Test.[112] In contrast, only patients with temporal seizures demonstrated improved verbal memory as tested on the Auditory Verbal Learning Test.[112] Similarly, although there were no significant impairments to cognition over 7 years in the DBS trial, improved patient scores in cognition were reported in only specific measures of attention and executive function.[98] The minimal changes to cognition in these paradigms may be attributed to the fact that stimulation target and parameters were specifically optimized with only seizure reduction in mind.

Novel Stimulation Parameters for Cognition and Epilepsy

The septohippocampal circuit and theta oscillations

Separate studies using unique anatomic targets have demonstrated the potential for neurostimulation to improve cognition in patients with neurologic disorders.[113,114] It is worth noting, however, that these studies yielded mixed results. Suthana and colleagues demonstrated that 50 Hz DBS of the entorhinal cortex resulted in improved spatial memory, whereas direct hippocampal stimulation did not.[114] However, in a study designed to validate these findings, stimulation of either entorhinal or hippocampal foci significantly impaired verbal and spatial memory.[115] Several other studies applying direct hippocampal stimulation also observed significant impairments to verbal memory.[116,117] In summary, although there has yet to be a major breakthrough, considerable effort has been directed at modulating cognitive function in patients with cognitive disability. However, these efforts have focused exclusively on improving cognition and have made no attempt to treat the underlying neurologic conditions, such as epileptic seizures.

One key to developing a successful intervention that can target both the underlying neurologic disorder and common comorbidities, such as spontaneous seizures and cognitive dysfunction in epilepsy, is to identify a single target that can modulate both processes. Several approaches using a single target have been considered. The hippocampus is a potential target to modulate seizures and cognition; in particular, it is a potential origin of temporal lobe seizures. However, this complex structure has multiple efferents and afferents and is a center for coordinating learning and memory-related information. Therefore, one of the complications of stimulating the hippocampus (or other inputs carrying complex and diverse information, such as the entorhinal cortex) is that stimulation may entrain one function while simultaneously silencing or interrupting others. For example, stimulation of either the hippocampus or entorhinal cortex can impair multiple measures of cognitive function.[115–117] Therefore, we propose that indirect circuit modulation may provide an effective alternative to entrain hippocampal activity, which can reduce seizures and promote cognition without silencing or otherwise altering other necessary processes. In fact, several studies have demonstrated some memory improvements resulting from hypothalamic/fornix stimulation.[113,118,119] Three critical findings resulted from these studies of alternate stimulation targets: (1) stimulation of the hypothalamus/fornix drives neural activity in structures important for learning and memory; (2) specific cognitive processes, such as autobiographical memory and spatial memory, can be improved as a result of stimulation; and (3) specific stimulation parameters (e.g., fornix/hypothalamus, high/low/theta burst frequencies) may be critical for certain brain processes.[113,118,119] Together, these experiments highlight the importance of adopting a network-level approach to identify alternative targets for stimulation and to focus on developing neurostimulation parameters that, combined with a common target, will improve both seizure control and cognitive outcome.[120]

Although the fornix includes fibers from multiple nuclei, one can also modulate one of the specific efferent hippocampal pathways contained within the bundle directly by stimulating the neurons within the MSN.[121–123] Fibers from the MSN project through the fornix into the hippocampus, with a reciprocal connection via the lateral septum.[121,124–128] In addition to neuronal intraconnectivity within the MSN and interconnectivity with the hippocampus, the combination of the septal nuclei and the hippocampus also projects broadly to many cortical and subcortical locations.[121,129–131]

One physiologic signature of the septohippocampal circuit that is observed across many regions related to seizures and cognition is the theta oscillation.[132] Theta oscillations (typically described as 3–8 Hz field potentials in humans, 6–10 Hz in a rat) result from synchronized changes in ionic movements and are known to play a key role in both seizure states and cognitive processes.[133–138] In a healthy brain, the septohippocampal circuit is one of the key modulators of theta oscillatory activity and is important for modulating both hippocampal excitation and inhibition.[122,139–141]

There is considerable evidence for the role of septohippocampal theta oscillations in cognitive processes in both rodents and humans. For example, in rodents, disruption of the MSN leads not only to reduced theta oscillations but also deficits in cognition.[136,142] Specifically, pharmacologic inactivation of the MSN using the anesthetic tetracaine significantly attenuates hippocampal theta power and is correlated with deficits in spatial tasks, such as the continuous

spatial alteration task on the T-maze,[137,143] the radial arm maze,[135] and the Morris water maze.[136] Recent work has demonstrated that theta oscillations are also critical for cognitive processes in humans.[144–147] For example, just as rats exhibit an increase in theta oscillations during spatial mazes, patients with implanted recording electrodes demonstrate increased hippocampal theta activity during virtual navigation tasks and episodic recall.[148,149] Similarly, hippocampal and parahippocampal theta oscillations are increased during goal-seeking navigation in a virtual version of the Morris water maze.[150] Notably, in a separate virtual reality task, patients continued to oscillate in theta frequency as they were teleported between known locations, receiving no visual information related to movement.[146] These data suggest that oscillations can be related to spatial processing in the absence of actual visual input or movement. In sum, there is clear evidence of a relationship between slow wave theta oscillations and cognitive processes not only in the rodent but also in humans.

The same circuit that is critical for the presence of theta oscillations and intact cognition is compromised in animals with epilepsy. Significant degeneration of septohippocampal neurons, specifically γ-aminobutyric acid (GABA)ergic interneurons, is evident both acutely following status epilepticus and chronically in animals treated with chemical convulsants such as pilocarpine.[151,152] Our lab has replicated key findings[151,153–156] that chronic EEG recordings from pilocarpine-treated epileptic rats implanted with depth electrodes in the hippocampus reveal a significant reduction in the power of hippocampal theta oscillations approximately 6 weeks following pilocarpine exposure (Fig. 2). Furthermore, there is evidence that the phase relationship between neurons of the septum and the hippocampal theta rhythm becomes uncoupled.[151,157–159] It is notable that altered oscillations coincide with impaired performance in spatial memory tasks, both acutely following induction of status epilepticus and at the chronic stage of epilepsy.[155,156,160–162] These results suggest that the theta oscillations critical for learning and memory are disrupted in epilepsy.

Antiepilepsy characteristics of theta oscillations

Previous studies have demonstrated the relationship between the presence of theta oscillations and reduced hyperexcitability in the septohippocampal circuit.[134,153] Injection of carbachol, a cholinergic agonist, induced theta oscillations and reduced both seizures and interictal spikes in rats exhibiting acute PTZ-induced seizures and chronically epileptic rats treated with pilocarpine.[134,153] In addition, in the PTZ model, stimulation of the MSN reduced ictal activity, whereas lesions to the same region increased seizure likelihood.[134] Epileptic spikes were also decreased as a result of physically (via rodent tail pinch) and electrically evoked theta oscillations.[153]

Stimulation of the MSN to reduce seizures and improve cognition

Because altered theta oscillations are apparent within the hippocampus of epileptic animals, we hypothesized that restoring oscillations via theta frequency stimulation (7.7 Hz) of the MSN could both be antiepileptic and

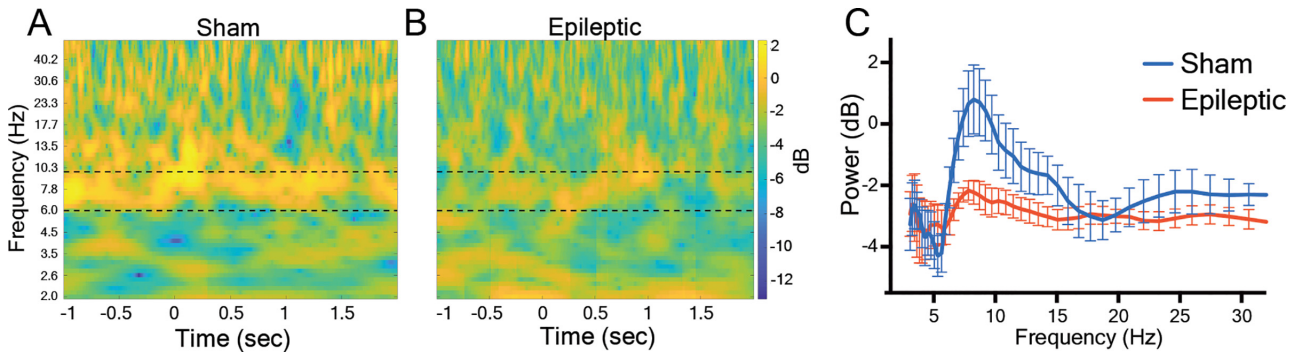

Figure 2.

Power analyses of experimental groups consisting of surgical controls labeled "Sham" (n = 5) and pilocarpine-induced epileptic animals labeled "Epileptic" (n = 7). All animals were implanted with tungsten electrodes in the MSN (stimulating) and the ventral hippocampus (recording). One week later, status epilepticus was induced via pilocarpine injection (350 mg/kg) 30 minutes following injection of scopolamine methyl nitrate (1 mg/kg). Convulsive seizures were terminated after 4 hours with injection of diazepam (8 mg/kg). All animals exhibited spontaneous recurring seizures in the weeks following pilocarpine injection. On day 45 following pilocarpine injection, baseline estimates of power were computed across a 5-minute behavioral test with animals exploring 2 novel objects. **A**, The group-averaged spectrogram for sham animals during specific 3-second epochs (1 second before and 2 seconds after interaction with an object) demonstrates increased power in the theta band relative to baseline. **B,** The group-averaged spectrogram for epileptic animals during comparable 3-second exploratory epochs did not demonstrate similar power in the theta band as compared to sham. **C**, Power spectral density plots are shown for both sham and epileptic animals. There was a significant difference in theta power as compared to baseline between sham and epileptic rats ($t(10) = 2.89$, $P < 0.05$).

improve cognition. Our hypothesis stemmed from 2 lines of preclinical studies: those demonstrating the ability to specifically drive hippocampal theta oscillations[163–167] and separate experiments focused on septal stimulation in animals with attenuated theta (either via chemical lesion or brain injury).[134,136,168,169] For example, Gray and Ball demonstrated that 7.7 Hz stimulation of the MSN represents the lowest threshold for driving hippocampal theta oscillations.[164] In addition, McNaughton and colleagues were able to evoke hippocampal theta oscillations and improve spatial learning via theta frequency stimulation of the fornix in rats with tetracaine-induced lesions to the MSN.[136] We have also previously demonstrated improved learning and memory as a result of 7.7 Hz MSN stimulation in the fluid percussion model of traumatic brain injury (TBI), although we did not show evidence of hippocampal oscillations during septal stimulation.[168,169] Theta frequency stimulation of the MSN in rats acutely following pilocarpine treatment, prior to the development of epilepsy, improved Barnes maze spatial navigation as compared to nonstimulated rats.[156] In a separate study, rats exhibiting spontaneously recurring seizures in the weeks following pilocarpine-induced status epilepticus were similarly tested on the Barnes maze spatial navigation task. To quantify seizure threshold, convulsive seizures were induced by exposure to flurothyl (bis(2,2,2-trifluroethyl) ether, a volatile $GABA_A$ antagonist. Critically, theta frequency stimulation of the MSN improved performance on the Barnes maze and concurrently increased seizure threshold during the flurothyl assay (Izadi, *In Review*). In addition, a 2015 review of MSN stimulation for TLE similarly supported septal neurostimulation for epilepsy, hypothesizing that stimulation of this region can prove effective in patients with refractory TLE.[97] Based on all of the reported data, we propose that the MSN represents a potential target, and theta a specific frequency, with the potential to both reduce seizures and improve cognitive outcome.

It is important to consider the variables associated with translating potential therapeutic paradigms from bench-to-bedside. For example, each of the 3 FDA-approved neurostimulation devices resulted in some degree of plasticity, as is suggested by improved seizure control over time. Critically, in patients with these devices, stimulation did not enhance the epileptic pathology, for example, by increasing lesion size or leading to enhanced seizures over time. Furthermore, in each of the devices that have been translated, the investigators have catalogued patients' responses not only in terms of seizures but also regarding common comorbidities such as cognition, mood disorders, and depression, as well as sudden unexpected death. Although there is evidence that stimulating theta oscillations can acutely promote cognition and reduce seizures, questions remain about chronic theta stimulation across the multiple domains of interest. It is critical to closely examine the risks and outcome measures of any new stimulation paradigm, septal or other, and to compare these with existing medical, surgical, and neurostimulation therapies.

Conclusion

More than one-third of patients with epilepsy, particularly focal epilepsies such as TLE, are refractory to pharmacologic treatment. Although resection remains the primary option for curative treatment, many patients do not meet surgical criteria, as they are multi-focal or have a seizure focus in a part of the brain that cannot be resected. Clinically approved stimulation paradigms such as VNS, RNS, and DBS represent reversible surgical interventions with the flexibility to treat many of the patients who do not meet resection criteria. Neurostimulation is a safe, well-tolerated treatment paradigm that progressively reduces seizures over time. Although neurostimulation therapies are effective at reducing seizures, they rarely eliminate them and should be considered therapeutic but not curative. To date, there is no stimulation target that can both reduce seizures and ameliorate epilepsy-related comorbidities such as cognitive dysfunction. In this review, we have proposed that modulating theta oscillations via MSN stimulation has the potential to reduce seizures, as well as to improve cognitive function. Ultimately, continued research into the optimization of potential neurostimulation paradigms will advance our ability to treat patients with refractory epilepsy by reducing seizures, ameliorating comorbidities, and improving overall quality of life.

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Disclosure

None of the authors has any conflict of interest to disclose. 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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