Closed-Loop Brain Stimulation and Paradigm Shifts in Epilepsy Surgery

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KEYWORDS

• Epilepsy surgery • Responsive neurostimulation • Closed-loop
• Deep brain stimulation • Stereo-electroencephalography • Local field potentials
• Seizure network

KEY POINTS

- Epilepsy surgery is underutilized.
- Responsive neurostimulation is Food and Drug Administration approved for focal epilepsy and is highly efficacious.
- Strategies and goals for diagnostic intracranial monitoring surgery have expanded.
- The role of the thalamus in different epilepsies is emerging.
- Generalized epilepsy may be treated effectively with intracranial neuromodulation.

INTRODUCTION

Epilepsy is the fourth most common neurologic disorder. In 2015, the Centers for Disease Control and Prevention estimated that there are at least 3.4 million people with epilepsy in the United States.[1] The cost to society of not optimizing the clinical care of these individuals is quite high. The annual direct medical cost of epilepsy in the United States is estimated to be at least $14 billion in today's dollars,[2] although that number excludes most of the cost burden, such as community service costs and indirect costs from losses in quality of life and productivity. Moreover, costs for individuals with drug-resistant epilepsy (DRE) are as many as 10 times greater than for those whose seizures are prevented by medication.[3]

Thirty percent to 40% of patients with epilepsy have DRE and therefore are surgical candidates.[4] Despite its potential to cure some types of epilepsy, surgery remains a vastly underutilized treatment, with only a small minority of candidates receiving surgical treatments. For example, the 2003 joint position paper from the American Academy of Neurology, American Association of Neurological Surgeons, and the American

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Epilepsy Society estimated that less than 3% of surgical candidates receive surgery, assuming 4000 epilepsy surgeries performed per year out of 150,000 potential surgical candidates.[5] Subsequent studies have demonstrated no change in epilepsy surgery utilization.[6–8] Moreover, the average time from diagnosis to surgery for a medically refractory patient is reported to be around 18 years, in data from both before and after the joint position paper's recommendation that the patient with DRE should be referred to a comprehensive epilepsy center. DRE is defined as the failure of only 2 appropriately considered medications.[9] Alarmingly, contrary to these guidelines, more than 75% of patients with DRE are not referred to an epilepsy specialist.[10] One of every 10,000 newly diagnosed people with epilepsy will die of sudden unexpected death in epilepsy (SUDEP),[10] but sadly the SUDEP rate is 90-fold higher in those with DRE.[10] Thus, underutilization of epilepsy surgery is a public health crisis that requires proactive intervention.

Traditional resective epilepsy surgery can be curative in many cases but is often viewed incorrectly as dangerous.[9] Surprisingly, 60% to 75% of neurologists are not aligned with epilepsy specialists on best referral practices, with obstacles to referral including knowledge deficits regarding the definition of DRE, existing practice guidelines, indications and timing for epilepsy surgery referral, and understanding the numerous types of epilepsies that are amenable to surgery.[11] It may be helpful that several advances have become mainstream over the last decade that increase surgical options for patients with focal epilepsy, while being minimally invasive. These options include intracranial neuromodulation devices that can record from the brain, providing highly useful chronic and patient-specific data. In addition, there is growing evidence that intracranial neuromodulation is efficacious in the treatment of some primary generalized epilepsies. Expeditious referral to a comprehensive epilepsy surgery program is imperative to enable individuals with DRE to have access to the full spectrum of modern surgical treatments (**Fig. 1**). In light of this gap between what is possible and the surgical care actually received by the average patient with DRE, this article reviews 5 paradigm shifts in epilepsy surgery that are useful to consider for optimizing treatment.

PARADIGM SHIFT: BEYOND SEIZURE FREEDOM—QUALITY OF LIFE

Curing a patient's epilepsy through resection of the seizure onset zone traditionally has been considered the only goal of epilepsy surgery. Given that patients with poorly localized focal epilepsy, focal epilepsy arising from eloquent cortex, and patients with primary generalized epilepsy are not candidates for resection, there is growing awareness that intracranial neuromodulation can produce meaningful quality-of-life improvements. The first Food and Drug Administration (FDA) -approved intracranial neuromodulation device for epilepsy was the responsive neurostimulation system (RNS). The RNS System ® (NeuroPace, Inc., Mountain View, CA) is a completely cranial implant, consisting of a programmable onboard processor with 4 recording channels coupled to 2 bidirectional leads capable of both recording and stimulating, as well as storing electrographic data for offline analysis. Since approval in 2013, several publications have described the long-term outcomes of patients who participated in both the feasibility and the pivotal clinical trials of RNS therapy. Nair and colleagues[12] reported outcomes from 162 patients who participated in these trials and completed 9 years of follow-up. The median percent reduction at the end of 3 years was 58%, improving to 75% by the end of 9 years of treatment. Importantly, 35% experienced $\geq$90% seizure reduction and 21% were seizure free in the last 6 months of follow-up. A separate publication tackled the question of whether the timing of clinical

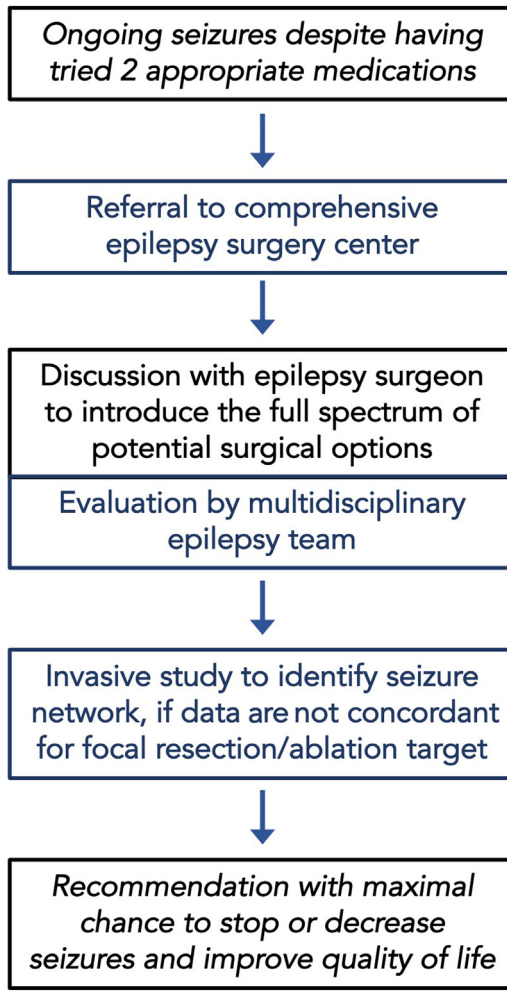

Fig. 1. Efficient presurgical evaluation. Individuals whose seizures are not controlled after having tried 2 appropriate medications should be referred for presurgical evaluation. Patients often benefit from an early introductory discussion with an epilepsy surgeon to explain how the presurgical evaluation is used to recommend a diagnostic and/or therapeutic surgery.

improvements in RNS therapy has accelerated in the field's posttrial experience. Based on a multicenter retrospective analysis, the answer appears to be yes: a median 75% seizure reduction was found at 2 years, and 82% reduction was achieved at $\geq$3 years.[13] The percentages of patients experiencing greater than 90% seizure reduction or no seizures in the last 6 months of follow-up also were similar to that previously reported at 9 years.

Deep brain stimulation (DBS) of the anterior nucleus of the thalamus (ANT), because of its involvement in common seizure propagating circuitry, was proposed by Upton and colleagues[14] for suppression of epileptiform discharges within the limbic system. In 1987, they reported significant seizure control in 4 of 6 patients with drug-resistant

complex partial seizures who underwent bilateral ANT stimulation.[15] ANT-DBS was FDA approved in 2018, with outcomes having been followed out to 10 years. At 7 years, median seizure frequency percent reduction from baseline was 75%.[16] It is important to note that patients in the pivotal trials for DBS and RNS were highly refractory, averaging an approximately 20-year history of epilepsy, 20 to 50 disabling seizures a month at baseline, and having failed multiple other epilepsy treatments.[12,17]

The benefit-versus-risk profile of intracranial neuromodulation is impressive. No intraparenchymal hemorrhages were reported in either pivotal trial.[17,18] The infection rate with RNS was 3% and with DBS was 10%, the latter's higher rate likely being secondary to the additional incisions and surgical site needed for DBS pulse generator placement in the chest. Remarkably, the SUDEP rate decreased by two-thirds for each therapy (~3 per 1000 patient-years), compared with the expected rate in the DRE population (~9 per 1000 patient-years). In addition to reduced seizure burden, low morbidity, and the prevention of mortality, these therapies produce measurable improvements in quality of life. Mean quality-of-life scores were significantly improved at 1 year for patients with RNS, and these improvements were maintained through at least 9 years of treatment.[12] For patients with DBS, improvements in quality of life at 5 years remained stable at 7 years, whereby 43% of subjects experienced a clinically meaningful improvement.[16] A separate study of the RNS clinical trial patients found no significant cognitive declines for any neuropsychological measure, whereas improvements were found in the Boston Naming Test and Rey Auditory Verbal Learning tests, in patients with neocortical and mesial temporal seizure onset zones, respectively.[19] Importantly, patients treated with RNS earlier in the course of their epilepsy exhibited significant improvements in multiple mood and quality-of-life measures that were not seen in patients treated later in the course of their disease, despite similar efficacy in seizure reduction.[20] Thus, quality-of-life data also support the need to apply urgency in the presurgical evaluation process.

PARADIGM SHIFT: EPILEPSY SURGERY AS NETWORK SURGERY

For several decades, there has been accumulating evidence that specific cortical and subcortical networks enable the onset and propagation of both partial and generalized-onset seizures.[21] The need to emphasize a network approach for epilepsy surgery in most American epilepsy centers stems from the deep-rooted tradition of considering primarily an electrical-anatomic, focus-oriented approach to epilepsy surgery. In the 1950s, Penfield and Jasper[22] established surface electrocorticography as the mainstay for defining an "epileptogenic focus," and Bailey and Gibbs[23] wrote that "surgical eradication of focal seizure activity was comparable to eradicating a tumor." In contrast, the stereo-electroencephalography (SEEG) philosophy originated by Talairach and Bancaud focuses on determining the regions of cortex generating the clinical manifestation of the seizure[24] whereby the chronologic occurrence of ictal clinical signs (semiology) is crucial for elucidating the "anatomo-electro-clinical" organization of seizures.[25] This approach facilitates the conception of seizures as an emergent property of brain networks and requires that epilepsy surgery address a patient's network rather than solely 1 potential focus.

Resecting a critical seizure network node that may render a patient seizure free is always the first treatment of choice, but a network-oriented approach may best prepare the clinical team to make that assessment (**Fig. 2**). One downfall of approaching epilepsy surgery solely from the perspective of focus hunting is that if a resection is performed and the patient is not seizure free, the interpretation is that one "didn't get enough" or did not find "the right focus." When the overall goal of epilepsy surgery

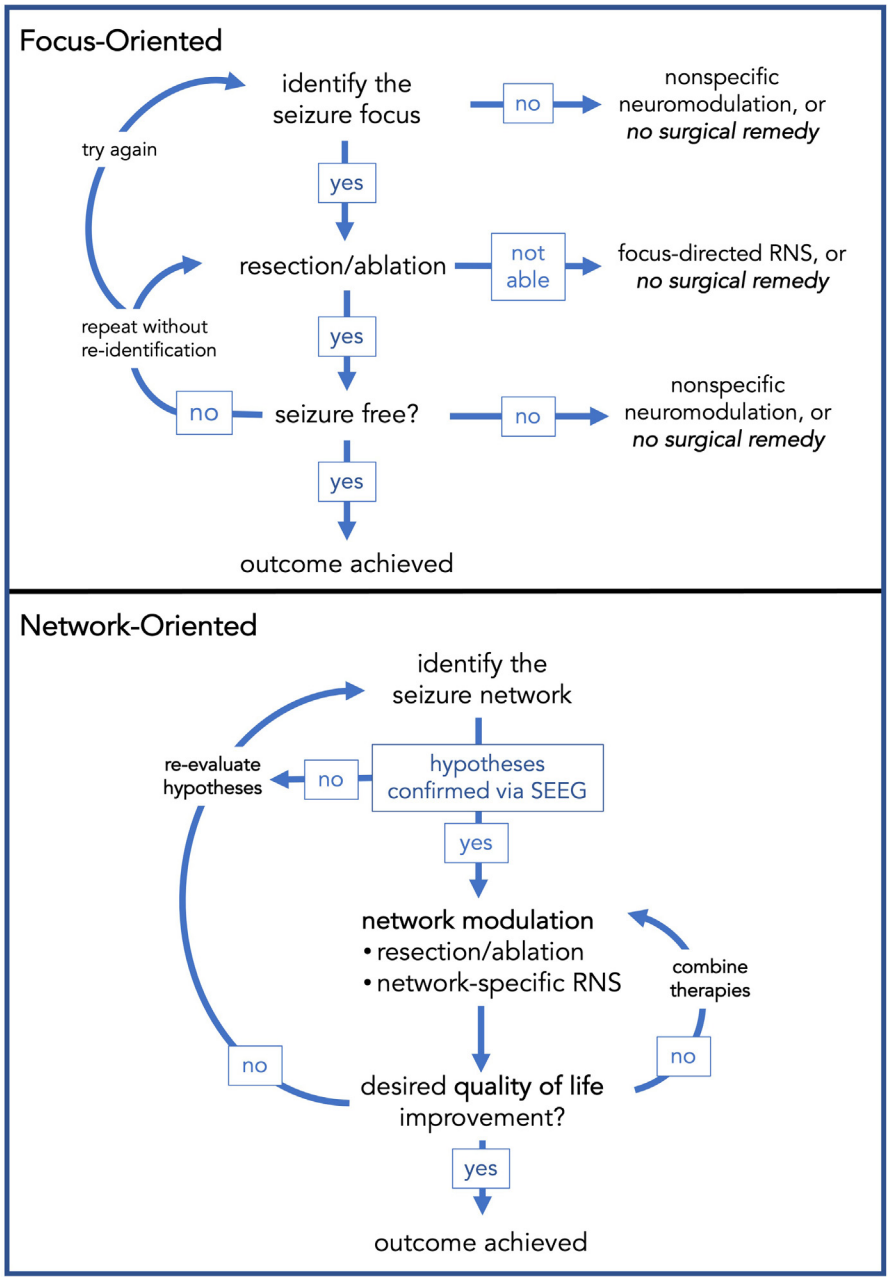

Fig. 2. Focus- versus network-oriented approaches to epilepsy surgery. A network-oriented surgical approach increases opportunities for therapeutic success.

is to take the seizure network offline, that is, to prevent emergence of seizures by disrupting the critical nodes of seizure organization, the emphasis is shifted from resection and seizure freedom to modulation and improved quality of life, with the ultimate goal of arresting seizures indefinitely. In addition, when the desired outcome of

intracranial monitoring extends beyond whether a resection can be accomplished and considers how to take the network offline, the opportunity to use more than 1 therapeutic approach is presented.[26] This type of multimodal surgical approach has been enabled by the advent of recent advances in epilepsy surgery in the United States: increased use of SEEG, the development of MRI-guided laser interstitial thermal therapy (LITT), and FDA approval of both RNS and ANT DBS. For instance, LITT may be used in combination with RNS.[26] Others have reported the upfront combination of open craniotomy for partial resection of the epileptogenic zone with implantation of RNS, in cases whereby the epileptogenic zone encompasses eloquent cortex.[27]

Regarding complex seizure networks, therapeutic modulation of difficult-to-localize, multifocal, or generalized epilepsies can be accomplished by influencing cortical seizure onset zones via diffuse cortical projections from the thalamus. This is the general premise underlying open-loop stimulation with ANT-DBS. Several groups have developed closed-loop paradigms using the RNS system, involving a recording contact in the thalamus, and a stimulating contact in the ANT,[28,29] centromedian nucleus (CM),[30,31] or pulvinar.[32] In the largest case series to date, Burdette and colleagues[31] reported the outcomes of 7 patients with regional neocortical focal seizures, treated with responsive cortical-CM thalamic stimulation. All patients achieved $\geq$50% reduction in disabling seizures, with 3 patients achieving greater than 90% reduction, at a median follow-up duration of 17 months. These investigators achieved similar results using responsive cortical-pulvinar stimulation to treat regional neocortical seizures having onsets in the posterior quadrant,[32] given the strong functional-anatomic connectivity between the pulvinar and posterior brain regions.[33] The fact that responsive stimulation in 3 different thalamic nuclei each could achieve greater than 50% seizure reduction in these highly refractory patients highlights the potential of attaining even better outcomes as techniques evolve and the understanding of the role of specific thalamic nuclei in a given individual's seizure network improves.

In a focus-oriented approach to epilepsy surgery, these outcomes without seizure freedom often are referred to as "palliative." Palliative means alleviating symptoms but not treating the underlying disease. Given the evidence that intracranial neuromodulation has a neuroplastic effect on brain circuitry,[34,35] and that multimodal therapy in multifocal epilepsy can take individual nodes offline, characterization of these therapies as palliative is incorrect and unhelpful. With a network-oriented approach, the goal of surgery is to reduce seizures as maximally as possible, whereby a clinically significant reduction in seizures after surgical therapy represents successful modulation of the seizure circuit. Whether seizure reduction in the absence of seizure freedom would improve the patient's quality of life to an extent that justifies the full application of available surgical therapies is an important component of the presurgical discussion between the patient and the multidisciplinary team. The practical implications of combining this philosophy with recent technological advances in surgical care is described in the following sections.

PARADIGM SHIFT: SURGICAL TREATMENT OF PRIMARY GENERALIZED EPILEPSIES

Given this favorable risk-benefit profile, attention in the intracranial neuromodulation field has expanded to primary generalized epilepsies, for which there currently is no FDA-approved surgical intervention. Likewise, the role of thalamic nuclei in generalized epilepsies has been a longstanding area of focus in both animal and human models, since the work of Hunter and Jasper,[36] who showed that seizures could be

induced by electrical stimulation of the thalamus. Subsequently, Monnier and colleagues[37] showed that medial thalamic stimulation could desynchronize cortical electroencephalography (EEG). In the 1980s, Velasco and colleagues[38–40] explored the CM as a DBS target for idiopathic generalized epilepsy (IGE), reporting excellent results. Subsequent feasibility studies and case series demonstrated equivocal findings, until a clinical trial by Valentín and colleagues[41,42] redemonstrated significant therapeutic benefit in patients with IGE. Recently, the University of Melbourne group reported results from a prospective, double-blind, randomized study of continuous, cycling stimulation of CM-DBS, in patients with Lennox-Gastaut syndrome.[43] The DBS device used in that study was not sensing-enabled, but subjects demonstrated significantly reduced electrographic activity on 24-hour ambulatory EEG at the end of the 3-month blinded stimulation phase.

Given that at least 20% of patients with IGE are refractory to pharmacologic treatment[44] (~35% of those with juvenile myoclonic epilepsy are refractory[45]) and evidence that the CM participates in the early propagation of generalized seizures, the author's group hypothesized that bilateral CM responsive neurostimulation with the RNS system would be effective in modulating the thalamocortical seizure network in individuals with IGE. Functional MRI studies have demonstrated increased signal in the thalamus both before[46] and at the onset of[47] generalized spike wave discharges (GSWD). Likewise, intracranial EEG (iEEG) recordings from externalized DBS leads implanted in patients with primary generalized epilepsy in previous studies have demonstrated that GSWD are present in the thalamus simultaneous with onset in the cortex.[48,49] The author reported the first use of bilateral CM RNS in a patient with IGE, a 19-year-old woman, diagnosed with eyelid myoclonia with absences.[50] iEEG recordings during the baseline prestimulation period revealed a multitude of transient (2- to 5-second duration) bilateral 3- to 5-Hz spike-wave discharges in the CM region, recapitulating the morphology and spectral signature of presurgical scalp EEG ictal discharges (**Fig. 3**). After 1 year of RNS therapy, the patient stopped taking all medications, and at 2 years, she continued to report a nearly 90% reduction in seizures, which manifest only as brief episodes of eyelid myoclonia, without loss of consciousness. The first 4 adult patients in the author's IGE CM-region RNS case series have all exhibited significant seizure reduction and improved quality of life (**Table 1**). Bilateral CM-RNS also has been reported in 2 pediatric patients with drug-resistant epilepsy secondary to Lennox-Gastaut syndrome and autism spectrum disorder,[51] and in a pediatric patient with primary generalized epilepsy,[52] all of whom experienced greater than 75% reduction in clinical seizures.

This intracranial neuromodulation experience in IGE demonstrates that it is important to think beyond the Engel score, which was created to assess outcomes relative to seizure freedom following surgical resection. The scale does not capture extensive quality-of-life changes that can occur in patients with intracranial neuromodulation without seizure freedom, such as a reduction in emergency room visits and hospitalizations, work/school days missed, and improvements in behavioral and developmental indices in younger patients. A multicenter, single-blind, randomized, sham stimulation-controlled pivotal study has been initiated with the goal of validating responsive thalamic stimulation as a surgical option for primary generalized seizures (NCT05147571).

PARADIGM SHIFT: VALUE OF CHRONIC INTRACRANIAL DATA

The advent of recording-enabled intracranial neuromodulation systems has opened an entirely new realm of clinical care in epilepsy, that of evaluating and responding

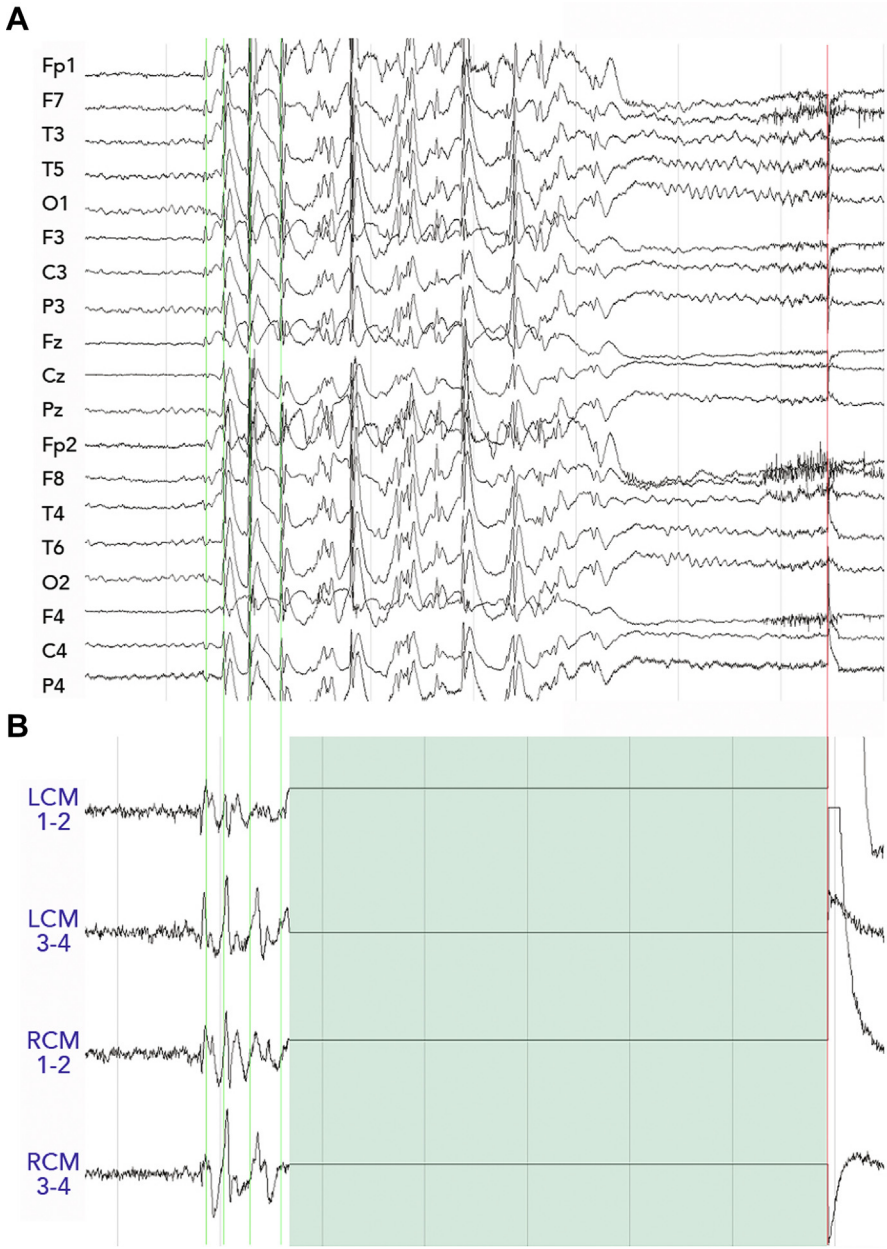

Fig. 3. Simultaneous scalp and iEEG recordings in an individual with IGE. Simultaneous scalp EEG (*A*) and intracranial thalamic EEG recordings on the 4 channels of the RNS device (*B*), during a generalized discharge, exhibit a similar pattern of GSWDs. Responsive stimulation (*green block*) is seen to suppress GSWDs in this example. LCM, left centromedian; RCM, right centromedian.

Table 1
First cohort of patients with idiopathic generalized epilepsy with 2-y follow-up after bilateral centromedian nucleus–region responsive neurostimulation

	Age					No. AEDs			Seizure Frequency			Seizure Severity	
Case	Seizure Onset	RNS Implant	Months Implanted	Sex	Seizure Type	Trialed	At RNS Implant	At MRFU	Pre-RNS	Post-RNS	Engel Score	Pre-RNS	Post-RNS
1	11	19	33	F	Absence with eyelid myoclonia	6	2	0	60/d	6/d	IB	4	2
2	11	22	27	M	Absence, GTC	9	4	2	3/wk, 1/mo	<1/mo, <1/y	IIA	5	2
3	16	21	25	F	Absence, GTC	3	1	1	3/wk, 2–4/m	<1/mo, <1/y	IIIA	5	2
4	17	31	24	F	Myoclonic, Absence, GTC	5	2	2	1/d, 1/wk, 1/y	<1/d, <1/wk, <1/y	IC	4	1

Abbreviations: F, female; GTC, generalized tonic clonic; M, male.

to data obtained from chronic iEEG recordings. The value of these data so far is evident in at least 6 domains: informing additional surgical procedures, seizure forecasting, medication management, lifestyle management, spell characterization, and biomarker detection.

Using iEEG recorded in 37 individuals with focal epilepsy implanted with RNS for up to 10 years, Baud and colleagues[53] first showed that interictal epileptiform activity oscillates with subject-specific multidien (multiday) periodicity, in addition to the well-known circadian rhythms. Seizures were found to occur preferentially during the rising phase of these multidien rhythms of interictal activity. In a follow-up study of 222 individuals with focal epilepsy implanted with RNS, it was reported that 60% of individuals exhibited multidien seizure cycles,[54] and 89% had a circadian cycle. This type of individualized data has the potential to greatly impact patients, given that self-reported and electrographic seizures occurred during the days-long rising phase of interictal activity, regardless of the length of the multidien period. Thus, it eventually should be possible to forecast the risk of seizure at any given timepoint to the patient, and additionally, to use this information to adjust medication timing to increase efficacy and reduce side effects.

Analysis of chronic iEEG data also can lead to evolution of the predominate seizure network hypothesis, enabling additional and highly effective surgery. Hirsch and colleagues[55] reported that among 157 patients with presumed bilateral epilepsy, 25 patients (16%) had a mesial temporal lobe resection informed by chronic ambulatory iEEG (mean duration of data storage = 24 months). Subsequently, the mean reduction in disabling seizures was 94% (range: 50%–100%) at last follow-up.

The ability to get an objective readout on medication efficacy and effects of medication adjustments in the patient's real-world environment also is unprecedented.[56] Quraishi and colleagues[57] recently demonstrated that in patients with RNS with stable detection settings, rates of interictal epileptiform and ictal detections predicted whether a new antiseizure drug would be efficacious, within the first 1 to 2 weeks. Given that most individuals with epilepsy are bothered constantly by physical or psychological effects of antiseizure medications,[58] the ability alone to track changes to medication, including medication withdrawal, can render RNS therapy worthwhile. The availability of this objective iEEG data creates the need for increased effort on the part of epilepsy practitioners. For example, gauging medication response by patient seizure report alone in an individual with RNS without looking at the data would be akin to flying an airplane without looking at the instruments. Fortunately, in the

United States, a procedure code (CPT 95836) has been developed that provides reimbursement for RNS iEEG review.

Patients with epilepsy also often experience episodic increases in seizure activity that sometimes are related to lifestyle choices. In 1 case, increased seizures were linked to increased caffeine consumption, by correlating trends in the iEEG data with the patient's behavior.[59] In that case, eliminating caffeine intake significantly reduced iEEG activity. Used in this manner, chronic iEEG monitoring can provide objective data with which to counsel patients regarding lifestyle choices in the areas of sleep hygiene, recreational drug use, and medication compliance. Similarly, the RNS system allows patients to trigger the storage of an iEEG record with use of a patient magnet that facilitates accurate characterization of patient-reported events, such as differentiating seizures from nonepileptic events, panic attacks, somatization disorders, and psychosis.[60]

Chronic iEEG recordings also are providing new opportunities to assess response to RNS therapy itself. Using RNS recordings from individuals with mesial temporal lobe implantations, Desai and colleagues[61] showed that the interictal spike rate was a strong differentiator of upper- versus lower-quartile clinical responders. Interictal spike rate was positively correlated with seizure rates at 7 years of therapy, suggesting that it could be used as a control signal to adapt stimulation delivered in a closed loop system. Kokkinos and colleagues[34] made the first discovery of putative ictal electrophysiological biomarkers that indicate and potentially predict therapeutic response in individual patients. By visually inspecting the spectral content of greater than 5000 RNS recordings that captured putative seizures, distinct categories of electrographic seizure pattern modulation (ESPM) were detected that were always present in responders and never present in nonresponders. In some cases, these ESPMs were observed in RNS recordings before patient-reported seizure reduction, suggesting their potential utilization in predicting therapeutic response. Subsequently, Khambhati and colleagues[35] identified another type of potential treatment response biomarker. By assessing interictal network reorganization during RNS therapy, they found that clinical seizure reduction was associated with changes in frequency-dependent functional connectivity within, between, and outside seizure foci. Since the extent of this reorganization scaled with seizure reduction and emerged within the first year of treatment, this network measure also may contribute to future strategies for prediction of therapeutic response.

In addition to the RNS system, a second sensing-enabled system with the ability for chronic recording of local field potentials is available clinically, the Medtronic Percept. The FDA-approved functionality of this system currently is limited to following the recording of peaks in the magnitude of the local field potential in the frequency domain (without ability for closed-loop stimulation), but other systems have been used in several preclinical studies of sensing-enabled DBS that explored the electrophysiology of seizure circuits in the time-frequency domain.[62–65] Use of the investigational Medtronic Summit RC+S research device, which can provide continuous iEEG (up to 1000 Hz) from any of 4 contacts on 4 leads, was recently reported for the optimization of automated seizure detection using ANT recordings, in individuals with bilateral ANT and hippocampus DBS leads.[66] This work presages opportunities that will emerge to characterize and modulate seizure networks, as device technologies evolve to include wireless data-streaming capabilities and increasing numbers of recording and stimulating channels.

PARADIGM SHIFT: GOALS AND STRATEGIES OF DIAGNOSTIC EPILEPSY SURGERY

The increased use of intracranial neuromodulation of both cortical and subcortical regions has expanded the scope of diagnostic epilepsy surgery. Given the safety profile

of intracranial neuromodulation, the different avenues it offers for potential improvement in quality of life, and its potential use in multifocal and generalized epilepsies, intracranial monitoring surgery, specifically SEEG, has evolved to test a broader range of hypotheses about seizure onset zones and networks. SEEG typically is more versatile for hypothesis testing than subdural grid implantation (unless the phase 1 data are overwhelmingly concordant with a surface lesion).[67,68] The ability to offer a surgical treatment that does not require choosing which brain region to resect has created the need to expand hypothesis testing about the seizure network in ways that inform clinical decisions involving intracranial neuromodulation (**Table 2**). If there is the potential for RNS therapy, one must consider whether sensing should occur in the same location as stimulation. For instance, the author's practice now incorporates thalamic monitoring during SEEG, in cases whereby an eventual recommendation for RNS seems more likely than resection alone, and when it is not clear whether there may be early thalamic involvement in the seizure onset. Others have also evaluated thalamic activity with SEEG to inform RNS implantation.[32] As 1 example, a 31-year-old man presented with a 30-year history of seizures having semiologies that suggested posterior frontal (left hand dystonia and left arm tonic posturing, head drops) and anterior frontal (hypermotor, integrated motor activity) onsets. His MRI showed bilateral extended polymicrogyria, and his ictal EEG showed diffuse onset. With this information, it was not clear whether the patient would be best suited for cortical RNS or where cortical leads would best be placed, versus potentially undergoing bilateral thalamic RNS. The SEEG implantation included leads targeting the CM bilaterally, to test the hypothesis that the thalamus was involved very early in seizure onset and thus would be appropriate to serve as a location for both seizure detection and stimulation. Leads were implanted using the same trajectory and orientation in which they

Table 2
Clinical scenarios in which thalamic implantation during stereo-electroencephalography informs surgical decisions

Clinical Scenario	SEEG Implantation	Seizure Onset Zone Interpretation	Surgical Options Informed by SEEG
1	Standard	Bilateral localized	Bilateral region-specific RNS, bilateral ANT DBS
	+ Thalamic	**Above with ETI**	**Above + bilateral thalamic RNS**
		Above without ETI	Bilateral cortical RNS, bilateral ANT DBS
2	Standard	Unilateral broad onset	Unilateral cortical RNS
	+ Thalamic	**Above with ETI**	**Above + unilateral thalamocortical RNS**
		Above without ETI	Unilateral cortical RNS
3	Standard	Bilateral multifocal onset	Bilateral cortical RNS, bilateral ANT DBS
	+ Thalamic	**Above with ETI**	**Above**
		Above without ETI	**Bilateral thalamic RNS**, bilateral ANT DBS
4	Standard	Primary generalized	Bilateral thalamic RNS, bilateral ANT DBS
	+ Thalamic	**CM > ANT at onset**	**Bilateral CM RNS**
		ANT > CM at onset	**Bilateral ANT DBS**

Bold text denotes changes in management informed by recording from the thalamus during intracranial monitoring.

Abbreviation: ETI, early thalamic involvement.

would be used if implanted therapeutically, in order to simulate recordings that would be captured by an RNS system in which the leads were implanted in a transfrontal approach (Fig. 4). In each seizure recorded, the onsets recorded from thalamic contacts were temporally indistinguishable from those recorded on cortical contacts (Fig. 5A), resulting in a recommendation for thalamic RNS. After implantation, seizures were detected readily (Fig. 5B). Using the thalamic signal to trigger stimulation, in cases such as this one, allows stimulation to affect widespread cortical networks, without having to choose a subterritory of cortex for detection and stimulation, as would be required with the placement of cortical leads. At 14 months of therapy, this patient's seizure frequency had been stably reduced from daily to weekly, with concomitant reduction in seizure severity.

Other centers have explored the value of including the thalamus in diagnostic SEEG surgery. The Marseille group reported very early involvement of the thalamus in 4 patients and delayed involvement in 7 patients, among 13 patients with temporal lobe epilepsy in whom an electrode contact had entered the thalamus through an extended cortical trajectory.[69] Likewise, the University of Alabama group reported data from 11 patients undergoing SEEG for suspected temporal lobe epilepsy, who were implanted in the ANT. Seizure onset was reported to be preceded by a decrease in the mean

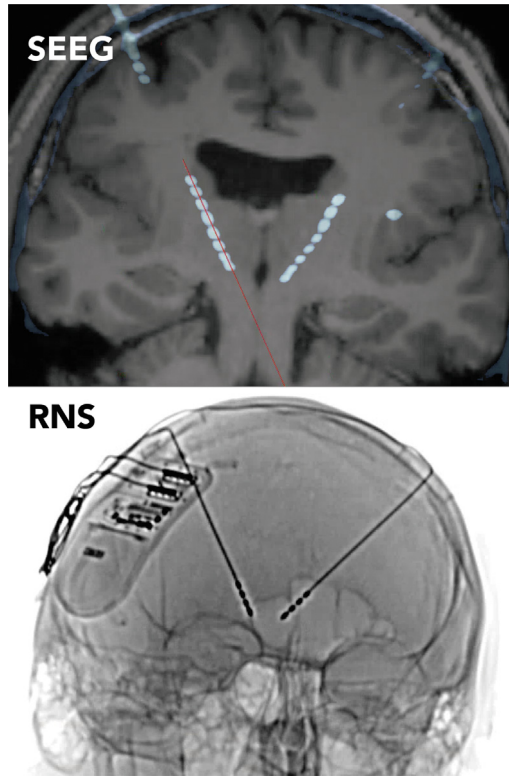

Fig. 4. Thalamic implantation during SEEG. Post-SEEG implantation CT fused to the preoperative brain MRI, demonstrating the position of the frontothalamic SEEG leads (*top*). The orientation and SEEG lead trajectories chosen for this patient were the same as that planned for use with transfrontal implantation of bilateral thalamic leads for RNS (*bottom*).

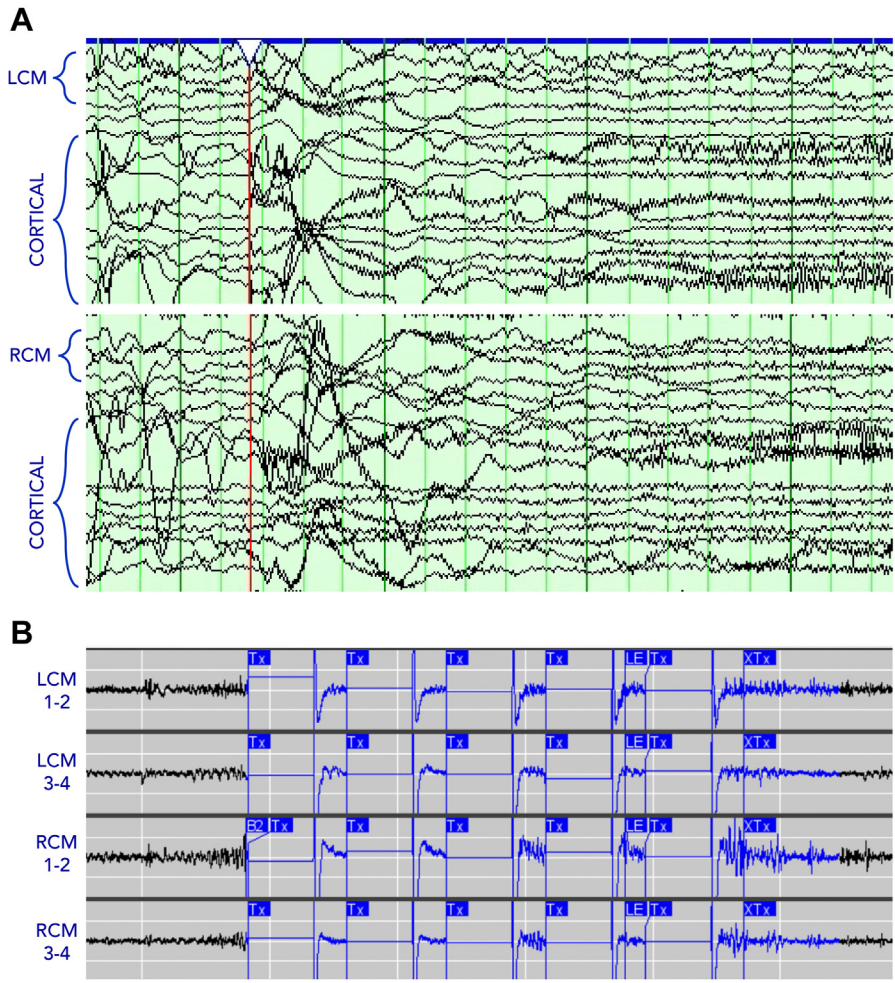

Fig. 5. Thalamic recordings during SEEG. (*A*) The thalamic contacts are active simultaneous with the cortical contacts at seizure onset. (*B*) Similar low-voltage fast activity subsequently was detected on the device and programmed to trigger stimulation.

power spectral density in both the thalamus and the seizure onset zone.[70] These investigators also observed early ictal recruitment of the midline thalamus in 3 cases of mesial temporal lobe epilepsy, where stimulation of either the thalamus or the hippocampus induced similar habitual seizures.[71] These results demonstrating the variable participation of thalamic nuclei in cases of temporal lobe epilepsy indicate the utility of mapping the involvement of potential thalamic nodes in an individual's seizure network, before including the thalamus in an intracranial neuromodulation strategy. Yu and colleagues[72] additionally demonstrated that high-frequency stimulation of the ANT during SEEG can desynchronize epileptic networks in a position-specific manner, implying that thalamic stimulation mapping may be useful for guiding clinically optimal lead placement.

Finally, it is important to note that although less frequent in epilepsy surgery before the approval of ANT-DBS, implantation of the thalamus and basal ganglia is an

everyday occurrence in movement disorders DBS surgery. Thus, there is a known safety profile for inserting leads in these subcortical structures,[73] most importantly, an approximately 1% chance of symptomatic hemorrhage.[74] This risk is not different from the general risk of hemorrhage in SEEG procedures.[75] Indeed, the safety of modifying the trajectory of 1 electrode planned for clinical sampling to extend to the thalamus, which obviates implanting an additional electrode for thalamic sampling, was recently described.[70] The event most likely to affect the clinical assessment may be a temporary lesion effect that can occur with thalamic implantation that could prevent the patient from having a seizure during the intracranial monitoring admission.[42]

SUMMARY

Approaches to the evaluation and surgical treatment of individuals with epilepsy are evolving, especially with regard to epilepsy networks, quality of life, primary generalized epilepsies, the utility of chronic intracranial recordings, and goals of diagnostic surgery. These paradigm shifts may facilitate closure of the surgical treatment gap in DRE.

CLINICS CARE POINTS

- Intracranial neuromodulation can reduce seizure frequency by 75%.
- Thalamic implantation in stereo-electroencephalography may inform intracranial neuromodulation treatment strategy.
- Implantation of the thalamus is safe.
- Responsive neurostimulation of the thalamus may be effective in treating idiopathic generalized epilepsy.

DISCLOSURE

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