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Closed-loop Brain Stimulation and Paradigm Shifts in Epilepsy Surgery

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Introduction

Epilepsy is the fourth most common neurological disorder. In 2015, the Centers for Disease Control estimated that there are at least 3.4 million people with epilepsy in the United States¹. 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 U.S. is estimated to be at least \$14B in today's dollars², 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. What's more, costs for individuals with drug-resistant epilepsy (DRE) are as many as ten times greater than for those whose seizures are prevented by medication³.

30–40% of epilepsy patients have DRE, and therefore are surgical candidates⁴. 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 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 candidates⁵. 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 both from before and after the joint position paper's recommendation that DRE patient should be referred to a comprehensive epilepsy center. DRE is defined as the failure of only two appropriately considered medications⁹. Alarming, contrary to these guidelines, more than 75% of DRE patients are not referred to an epilepsy specialist¹⁰. One of every 10,000 newly diagnosed people with epilepsy will die of sudden unexpected death in epilepsy (SUDEP)¹⁰,

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but sadly the SUDEP rate is 90-fold higher in those with DRE¹⁰. 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 dangerous⁹. Surprisingly, 60–75% of neurologists are not aligned with experts 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 surgery¹¹. 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. In light of this gap between what is possible and the surgical care actually received by the average DRE patient, this paper will review five paradigm shifts in epilepsy surgery that are useful to consider for optimizing treatment.

Paradigm Shift: Epilepsy surgery as network surgery

The need to shift to 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 established surface electrocorticography (ECoG) as the mainstay for defining an “epileptogenic focus,”¹² and Percival Bailey wrote that surgical eradication of focal seizure activity was comparable to eradicating a tumor.¹³ In contrast, the stereo-electroencephalography philosophy originated by Talairach and Bancaud focuses on determining the regions of cortex generating the clinical manifestation of the seizure¹⁴ where the chronological occurrence of ictal clinical signs (semiology) is crucial for elucidating the “anatomy-electro-clinical” organization of seizures¹⁵. 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 one 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. 1). 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 didn’t find “the right focus.” With an overall goal of epilepsy surgery is to take the seizure network offline, i.e. 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. Additionally, when the desired outcome of intracranial monitoring extends beyond whether or not a resection can be accomplished and considers how to take the network offline, the opportunity to use more than one therapeutic approach is presented¹⁶. This type of multi-modal 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 responsive neurostimulation (RNS) and anterior nucleus of the thalamus (ANT) deep brain stimulation (DBS). For instance, LITT may be used in combination with RNS¹⁶. Others have reported the upfront combination of open craniotomy for partial resection of the epileptogenic zone with implantation of RNS, in cases where the epileptogenic zone encompasses eloquent cortex¹⁷. In the focus-oriented approach, 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^{18,19}, 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, where 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 multidisciplinary team. The practical implications of combining this philosophy with recent technological advances in surgical care is described in the following sections.

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 FDA-approved intracranial neuromodulation device for epilepsy was the Responsive Neurostimulation System (RNS). The RNS system is a completely cranial implant, consisting of a programmable onboard processor with four recording channels coupled to two bi-directional leads capable of both recording and stimulating, as well as storing a subset of information for offline analysis. Since approval in 2013, several publications have described the long-term outcomes of patients who participated in both the feasibility and pivotal clinical trials of RNS therapy. Nair and colleagues²⁰ 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 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 improvements in RNS therapy has accelerated in the field’s post-trial experience. Based on a multi-center retrospective analysis, the answer appears to be yes: a median 75% seizure reduction was found at 2 years, and 82% reduction was achieved at 3 years²¹. The percentages of patients experiencing >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), due to its involvement in common seizure propagating circuitry, was proposed by Cooper and Upton for suppression of epileptiform discharges within the limbic system²². In 1987, they reported significant seizure control in 4 of 6 patients with drug-resistant complex partial seizures

who underwent bilateral ANT stimulation²³. ANT-DBS was FDA-approved in 2018, with outcomes having been followed out 10 years. At 7 years, median seizure frequency percent reduction from baseline was 75%²⁴. 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, 20–50 disabling seizures a month at baseline, and having failed multiple other epilepsy treatments^{20,25}.

The benefit vs. risk profile of intracranial neuromodulation is impressive. No intraparenchymal hemorrhages were reported in either pivotal trial^{25,26}. 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 to 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 RNS patients, and these improvements were maintained through at least 9 years of treatment²⁰. A separate study of patients who completed the randomized control trial found no significant cognitive declines for any neuropsychological measure, while improvements were found in the Boston Naming Test and Rey Auditory Verbal Learning tests, in patients with neocortical and mesial temporal seizure onset zones, respectively²⁷. For DBS patients, improvements in quality of life at 5 years remained stable at 7 years, where 43% of subjects experienced a clinically meaningful improvement²⁴.

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, who showed that seizures could be induced by electrical stimulation of the thalamus²⁸. Subsequently, Monnier *et al.* showed that medial thalamic stimulation could desynchronize cortical electroencephalography (EEG)²⁹. In the 1980s, Velasco and colleagues explored the centromedian nucleus (CM) as a DBS target for idiopathic generalized epilepsy (IGE), reporting excellent results^{30–32}. Subsequent feasibility studies and case series demonstrated equivocal findings, until a clinical trial by Valentin *et al.* redemonstrated significant therapeutic benefit in IGE patients^{33,34}. 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 (LGS)³⁵. 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 IGE patients are refractory to pharmacological treatment³⁶ (~35% of those with juvenile myoclonic epilepsy are refractory³⁷) and evidence that the CM participates in the early propagation of generalized seizures, our group hypothesized

that bilateral CM responsive neurostimulation with the RNS system would be effective in IGE. fMRI studies have demonstrated increased signal in the thalamus both prior to³⁸ and at the onset of³⁹ generalized spike wave discharges (GSWD). Likewise, iEEG recordings from externalized DBS leads implanted in primary generalized epilepsy patients in previous studies have demonstrated that GSWD are present in the thalamus simultaneous with onset in the cortex^{40,41}. We reported the first use of bilateral CM RNS in a patient with IGE, a 19-yr-old female, diagnosed with eyelid myoclonia with absences⁴². iEEG recordings during the baseline pre-stimulation period revealed a multitude of transient (2–5 s duration) bilateral 3–5 Hz spike-wave discharges in the CM region, recapitulating the morphology and spectral signature of presurgical scalp EEG ictal discharges (Fig.2). After one 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 our 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 a pediatric patient with primary generalized epilepsy, resulting in complete resolution of daily absence seizure activity and 75% reduction in convulsive seizures⁴³.

The IGE experience 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 intracranial neuromodulation patients 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 to data obtained from chronic iEEG recordings. The value of this data so far is evident in at least three domains: seizure forecasting, medication management, and biomarker detection.

Using iEEG recorded in 37 individuals with focal epilepsy implanted with RNS for up to 10 years, Baud et al.⁴⁴ first showed that interictal epileptiform activity oscillates with subject-specific multidien (multi-day) 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 cycles⁴⁵ 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.

The ability to get an objective read-out on medication efficacy and effects of medication adjustments in the patient's real-world environment is unprecedented⁴⁶. Quraishi et al. recently demonstrated that in RNS patients with stable detection settings, rates of interictal epileptiform and ictal detections predicted whether a new antiseizure drug would be efficacious, within the first 1–2 weeks⁴⁷. Given that most individuals with epilepsy are bothered constantly by physical or psychological effects of antiseizure medications⁴⁸, the ability alone to track changes to medication, including medication withdrawal, can render RNS therapy worthwhile. The availability of this objective iEEG data does create the need for increased effort on the part of epilepsy practitioners. For example, gaging 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.

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 et al. 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 et al. made the first discovery of putative ictal electrophysiological biomarkers that indicate and potentially predict therapeutic response in individual patients¹⁸. By visually inspecting the spectral content of >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 non-responders. In some cases, these ESPMs were observed in RNS recordings prior to patient-reported seizure reduction, suggesting their potential utilization in predicting therapeutic response. Subsequently, Khambhati et al. identified another type of potential treatment response biomarker¹⁹. 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 pre-clinical studies of sensing-enabled DBS that explored the electrophysiology of seizure circuits in the time-frequency domain^{49–52}. Use of the investigational Medtronic Summit RC+S research device, which can provide continuous iEEG (up to 1000Hz) from any of four contacts on four leads, was recently reported for the optimization of automated seizure detection using ANT recordings, in individuals with bilateral ANT and hippocampus DBS leads⁵³. 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 stereo-electroencephalography (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 is overwhelmingly concordant with a surface lesion)^{54,55}. 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 where an eventual recommendation for RNS seems more likely than resection alone, and when it's not clear whether there may be early thalamic involvement in the seizure onset. As one 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 centromedian nucleus 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 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. 3). In each seizure recorded, the onsets recorded from thalamic contacts were temporally indistinguishable from those recorded on cortical contacts (Fig. 4A), resulting in a recommendation for thalamic RNS. After implantation, seizures were detected readily (Fig. 4B). 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 sub-territory 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 trajectory⁵⁶. Likewise, the University of Alabama group reported data from eleven 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 power spectral

density in both the thalamus and seizure onset zone.⁵⁷ These investigators also observed early ictal recruitment of the midline thalamus in three cases of mesial temporal lobe epilepsy, where stimulation of either the thalamus or hippocampus induced similar habitual seizures⁵⁸. 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, prior to including the thalamus in an intracranial neuromodulation strategy. Yu et al. 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 placement⁵⁹.

Finally, it is important to note that although less frequent in epilepsy surgery prior to 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 structures⁶⁰, most importantly an approximately 1% chance of symptomatic hemorrhage⁶¹. This risk is not different than the general risk of hemorrhage in SEEG procedures⁶². Indeed, the safety of modifying the trajectory of one electrode planned for clinical sampling to extend to the thalamus, which obviates the need to implant an additional electrode for thalamic sampling, was recently described⁵⁷. 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 admission³⁴.

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 drug-resistant epilepsy.

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Key Points

- Epilepsy surgery is underutilized.
- Responsive neurostimulation is FDA-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 a surgical target for brain stimulation.

Synopsis

Advances in device technology have created greater flexibility in treating seizures as emergent properties of networks that exist on a local to global continuum. All patients with drug-resistant epilepsy are potential surgical candidates, given that intracranial neuromodulation through deep brain stimulation (DBS) and responsive neurostimulation (RNS) can reduce seizures and improve quality of life, even in multifocal and generalized epilepsies. To achieve this goal, indications and strategies for diagnostic epilepsy surgery are evolving. This paper describes the state-of-the-art in epilepsy surgery and related changes in how we define indications for diagnostic and therapeutic surgical intervention.

Clinics Care Points

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

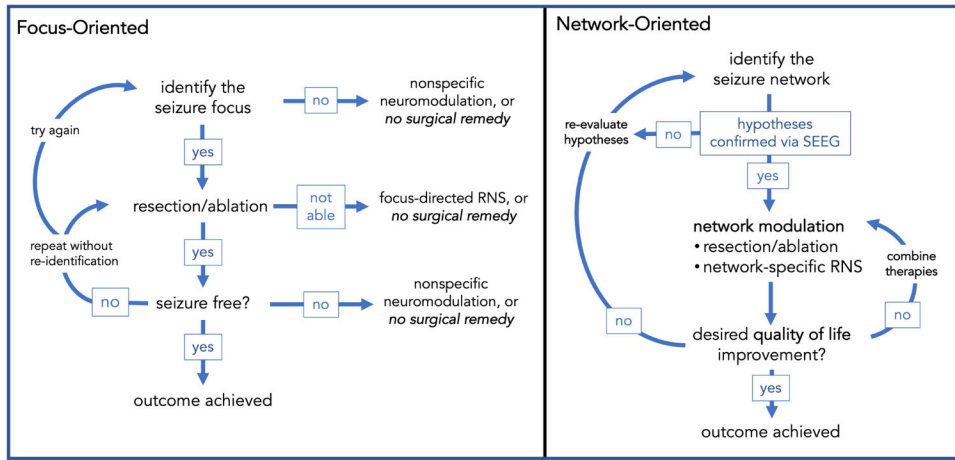


Figure 1. A network-oriented surgical approach increases opportunities for therapeutic success.

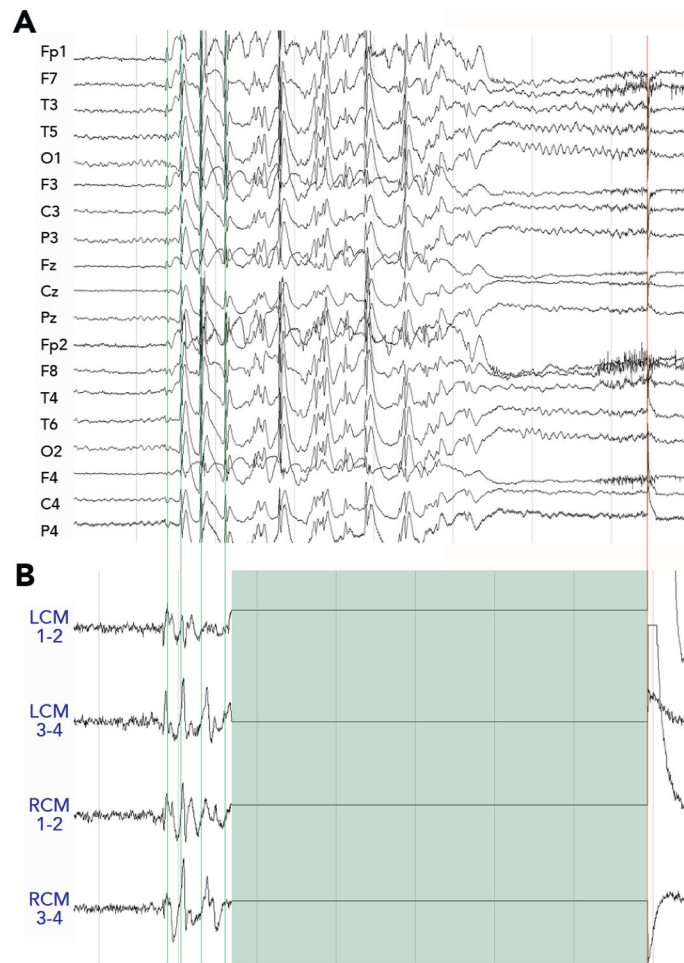


Figure 2. Simultaneous scalp and intracranial EEG recordings in an individual with IGE. Simultaneous scalp EEG (A) and intracranial thalamic EEG recordings on the 4 channels of the RNS device (B), during a generalized discharge, exhibit a similar pattern of GSWDs. Responsive stimulation (green block) is seen to suppress GSWDs in this example. LCM = left centromedian; RCM = right centromedian.

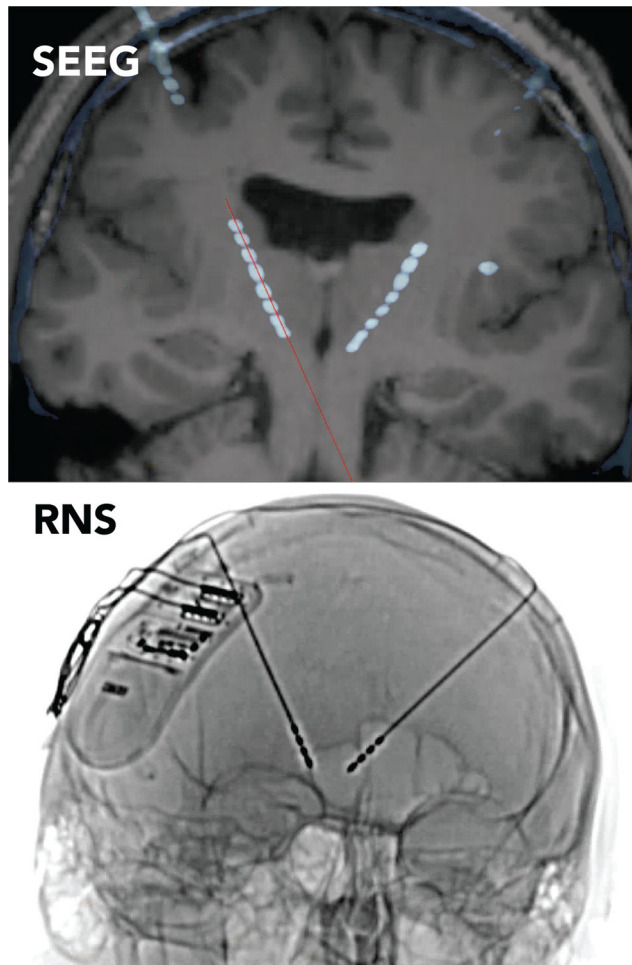


Figure 3. Thalamic implantation during SEEG.

Post-SEEG implantation CT fused to the pre-operative brain MRI, demonstrating the position of the fronto-thalamic 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).

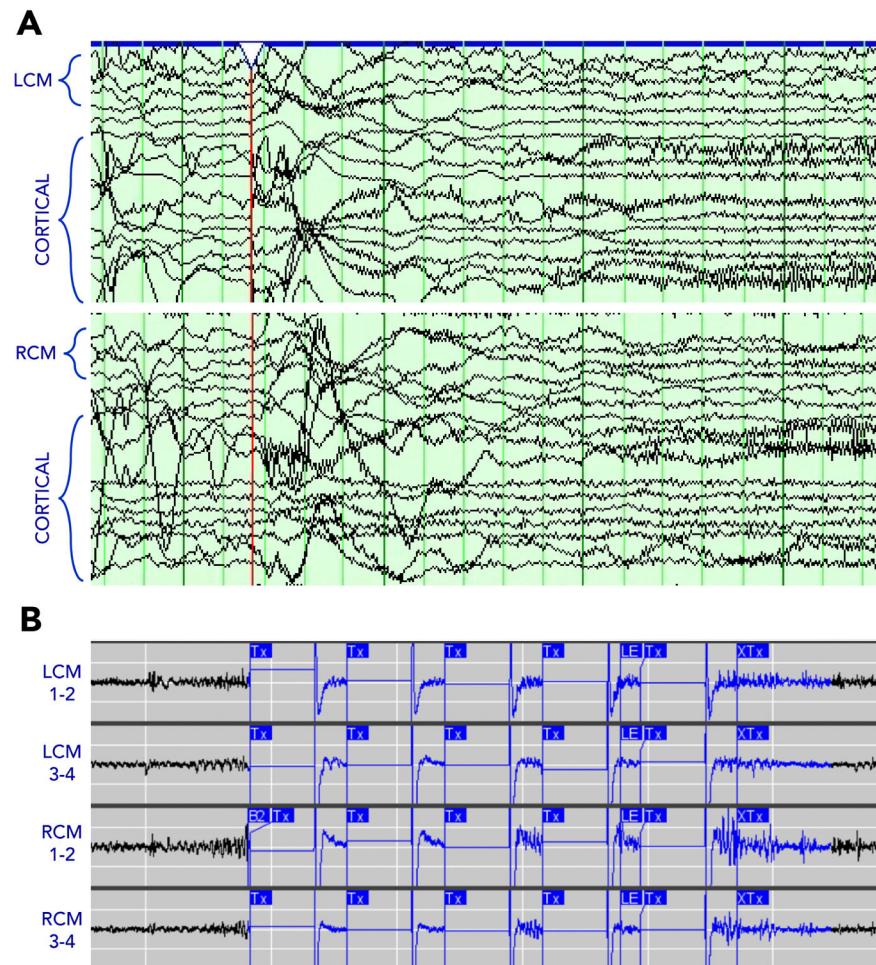


Figure 4. Thalamic recordings during SEEG.

The thalamic contacts (LCM, left centromedian; RCM, right centromedian) are active simultaneous with the cortical contacts at seizure onset. Similar low-voltage fast activity subsequently was detected on the device and programmed to trigger stimulation.

Table 1.

First cohort of IGE patients with 2-year follow up after bilateral CM-region RNS

Case	Age		Months implanted	Sex	Seizure type	#AEDs			Seizure frequency		Engel Score	Seizure severity	
	seizure onset	RNS implant				trialed	at RNS implant	at MRFU	Pre-RNS	Post-RNS		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/year	IIA	5	2
3	16	21	25	F	Absence, GTC	3	1	1	3/wk, 2-4/m	<1/mo, <1/year	IIIA	5	2
4	17	31	24	F	Myoclonic, Absence, GTC	5	2	2	1/d, 1/wk, 1/year	<1/d, <1/wk, <1/year	IC	4	1

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Table 2.

Clinical scenarios in which thalamic implantation during SEEG 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 thalamo-cortical 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

ETI = early thalamic involvement