Decision Making in Epilepsy Surgery

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KEYWORDS

• Epilepsy networks • Epilepsy surgery • Stereo-EEG • Responsive neurostimulation

KEY POINTS

Viewing epilepsy surgery as network surgery enables optimal consideration of

- Indications and methods of intracranial monitoring.
- Potential role of subcortical structures in seizure organization and propagation.
- Upfront use of combinatorial therapies to prevent seizure emergence from the network.
- Use of neuromodulation in novel epilepsy indications.

INTRODUCTION

The phrase "epilepsy is a network disorder" is often bandied about, but the practical implications of using this concept are far-ranging and sometimes overlooked. First, the network approach suggests that we conceive of a seizure as an emergent property of the brain.[1] What does that mean? Complexity theory describes emergence as the sudden appearance of new forms of organization that are not predicted by properties of individual elements but arise from self-organization.[2] The complexity approach was originally applied in meteorology, to explain how a highly organized storm could be created by a cascading series of interactions that originated from small, sporadic, and distant changes in wind currents. Seizures have similar nonlinear dynamics that are "related to but transcend the capacities of the neurons that create them."[3] In this article, I suggest that viewing epilepsy surgery as network surgery enables optimal consideration of the (1) need for and method of intracranial monitoring, (2) potential role of subcortical structures in seizure organization and propagation, (3) upfront use of combinatorial therapies to prevent seizure emergence from the network, and (4) use of neuromodulation in novel epilepsy indications.

The need to emphasize the network concept arises from the fact that the traditional surgical philosophy in American epilepsy centers involves an electrical-anatomic, focus-oriented approach. Since the time of Penfield and Jasper until recently, electrocorticography (ECoG) has been the mainstay for defining an "epileptogenic focus." Indeed, in one of the first reports of the use of ECoG in temporal lobe epilepsy surgery, Bailey and Gibbs[4] wrote that "the problem faced by the neurosurgeon in trying to eradicate focal seizure activity is comparable to that of trying to eradicate a neoplasm." In contrast, the stereoelectroencephalography (SEEG) philosophy developed by Talairach and Bancaud focused on using electrophysiology to determine the regions of cortex generating the clinical manifestation of the seizure.[5] In this context, the type and chronologic occurrence of ictal clinical signs (semiology) is crucial for elucidating the "anatomo-electro-clinical" organization of seizures.[6] Refinement of this approach over time, including incorporation of a variety of noninvasive imaging modalities, has resulted in 3-dimensional conceptualization of the network becoming an essential piece of epilepsy surgery planning.[7]

DECISION POINTS

Intracranial Monitoring

A significant problem with approaching epilepsy surgery from the perspective of focus-hunting, is

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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." This type of interpretation may often be flawed from the start. In contrast, if the overall goal of epilepsy surgery 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. 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 best prepares one to make that assessment.

One of the most critical decision points in epilepsy surgery is the choice and manner of implementing intracranial monitoring. The chosen strategy should test hypotheses about the seizure network that arise from the phase I noninvasive evaluation, and these hypotheses should be anatomically precise.[8] SEEG is much more versatile for hypothesis testing than subdural grid implantation, unless the phase 1 data are overwhelmingly concordant with a surface lesion (especially one that involves eloquent cortex). The general superiority of SEEG over subdural grids for network assessment was well characterized in the recent study by Tandon and colleagues,[9] who compared their extensive experience with both techniques. Their analysis of 239 patients found that therapeutic procedures following SEEG were associated with better outcomes (76% vs 55% Engel class I or II at 1 year), and this effect difference was amplified when considering only nonlesional cases (69% vs 35%). Indeed, use of SEEG resulted in a lower rate of patients undergoing resection and a higher rate of good outcomes, likely achieving an important goal of limiting the numbers of patients who lose cognitive function but continue to have seizures.

Multimodal Surgical Therapy

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 presented (Fig. 1). The following case illustrates this point.

A 34-year-old, left-handed woman presented with a 26-year history of epilepsy (onset at 8 years old). Her seizures were characterized by an aura described as visual change "almost like things are pixilated," voices sounding different, and eye blinking a few seconds later. Her clinical seizures progressed with loss of awareness, chewing, head turning to the right, and generalized tonic-clonic movements of less than 1-minute duration. Postictally, she could experience migraine headaches, nausea, and confusion. The frequency of these clinical seizures was 1 to 3 per week.

Phase 1 evaluation revealed an interictal encephalogram (EEG) with bursts of generalized disorganized sharp waves, maximal at left temporal or bi-frontotemporal contacts and lasting 2 to 5 seconds. The seizure onset was not localizable in the first few seconds of ictal EEG recordings, but left temporal evolution provided localization for the observed semiology (eg, chewing and right head turn). PET imaging demonstrated broad left hemisphere hypometabolism, most prominent in

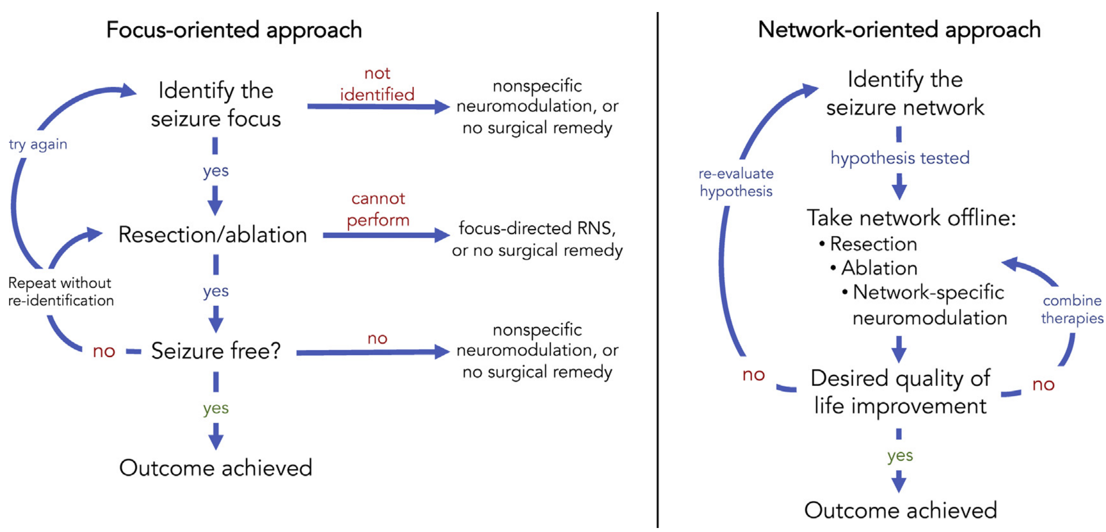

Fig. 1. Escaping the cycle of focus-chasing. Schematic representing the increased opportunities for therapeutic success inherent to a network-oriented surgical approach.

the temporal-occipital region (Fig. 2). Magnetoencephalography (MEG) source localization demonstrated dipole clusters in the left medial temporal lobe (see Fig. 2). From the phase 1 data, a primary hypothesis of left posterior temporal neocortical onset with rapid generalization was derived. Secondary hypotheses were left occipital versus left mesial temporal onset.

Phase 2 evaluation was carried out using SEEG to target a left temporal-occipital network. Two spontaneous seizures were captured. The first originated in the hippocampus (Fig. 3), and the second originated in the mesial-occipital lobe (lingual gyrus) (Fig. 4). Stimulation mapping with 50 Hz, 250 μs, 3 s trains produced the patient's typical visual aura in multiple occipital locations (current range = 1.5 to 4 mA) (Fig. 5). Hippocampal stimulation using the same frequency and pulse width produced a seizure at 1.5 mA (Fig. 6). Stimulation with 1 Hz, 1 μs, 30 s trains produced no changes at any stimulation locations. Thus, 2 epileptogenic zones were discovered: mesial-occipital, producing the patient's typical aura and generalization, and hippocampal, producing a milder seizure type recently recognized by the patient. Given that resection of both epileptogenic zones was not feasible, due to their broad nature across 2 contiguous lobes in the dominant hemisphere, a recommendation was made for upfront combinatorial therapy. The patient underwent SEEG lead removal, then returned 2 weeks later for hippocampal laser thermal ablation (Fig. 7). Two weeks after her ablation, the patient underwent responsive neurostimulation (RNS) implantation of 2 depth leads in the occipital lobe (see Fig. 7). Neither procedure would have been expected to render the patient seizure free or to significantly disrupt the remaining seizure network, thus there was no intervening assessment period between procedures. This patient reported a 50% to 74% reduction in seizures at 1-year postimplantation.

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 thermal ablation, and Food and Drug Administration approval of both RNS and anterior nucleus of the thalamus (ANT) deep brain stimulation (DBS). Other experts have reported the upfront combination of open craniotomy for partial resection of the epileptogenic zone with implantation of RNS, in cases were the epileptogenic zone encompasses eloquent cortex.[10] These 5 patients were included in the analysis of a cohort of 30 total patients receiving RNS for regional-onset seizures, in which 75% median reduction in clinical seizure frequency was observed over a median follow-up of 21 months.[10] In the focus-oriented approach, these outcomes without seizure freedom often have been described as "palliative," which means alleviating symptoms but not treating the underlying disease. The use of this word in the context of epilepsy surgery, however, should be abandoned. With a network-oriented approach, the goal of surgery is to reduce seizures as maximally as possible, where any reduction in seizures after surgical therapy represents successful modulation of the seizure circuit. In the absence of seizure freedom, whether the reduction of seizures obtained 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. This exact balance is always unknown, but the primary concern regarding the recommendation to the patient should be whether the network hypothesis has been optimally considered and tested.

This approach requires the surgeon to truly become a surgical neurologist, in the same way increasing use of molecular biology in the brain tumor field requires that neurosurgeons interested in

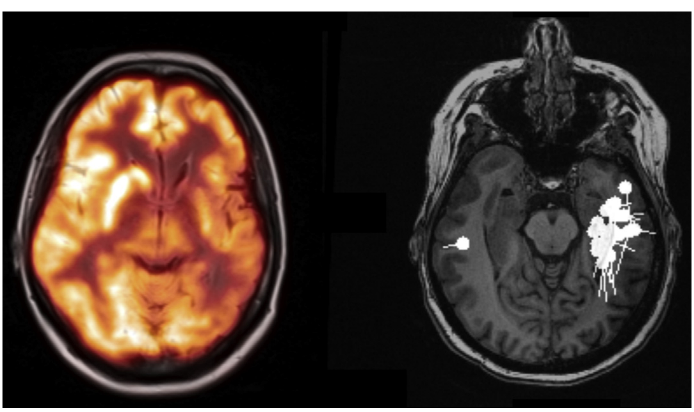

Fig. 2. Case example: preoperative imaging. The most relevant axial slices of the PET (*left*) and MEG (*right*) scans are shown.

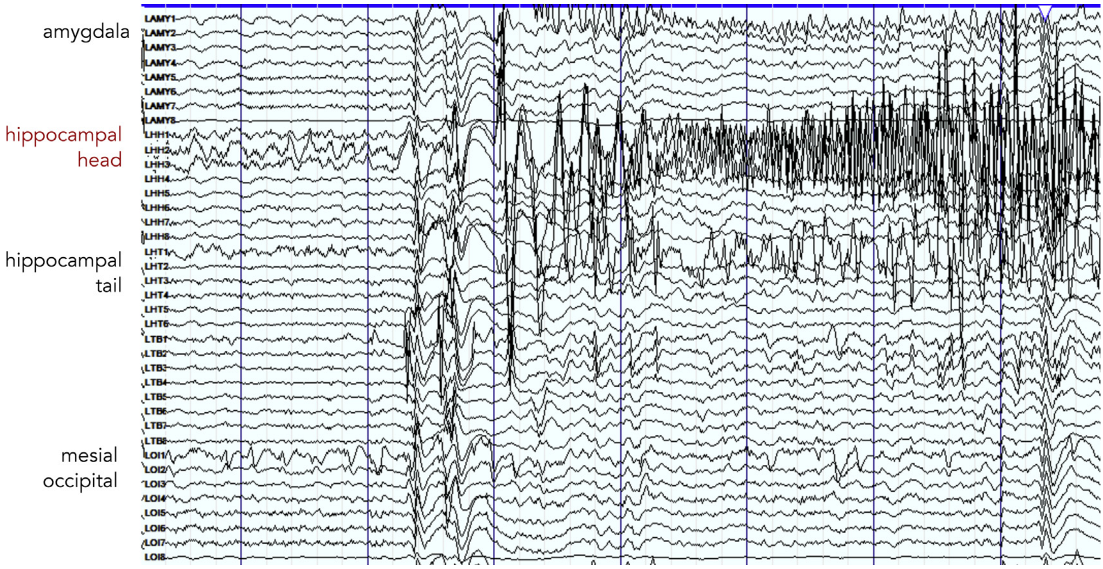

Fig. 3. Case example: seizure 1. Intracranial EEG recording of ictal onset in the anterior hippocampus.

making the best decisions for their patients act as surgical oncologists, rather than limiting their thinking to the technical aspects of excising the tumor. The ability to confidently make recommendations to the patient at each stage of the process of compressive diagnostic and therapeutic surgery is dependent on one's ability to assess the extent to which a given epilepsy

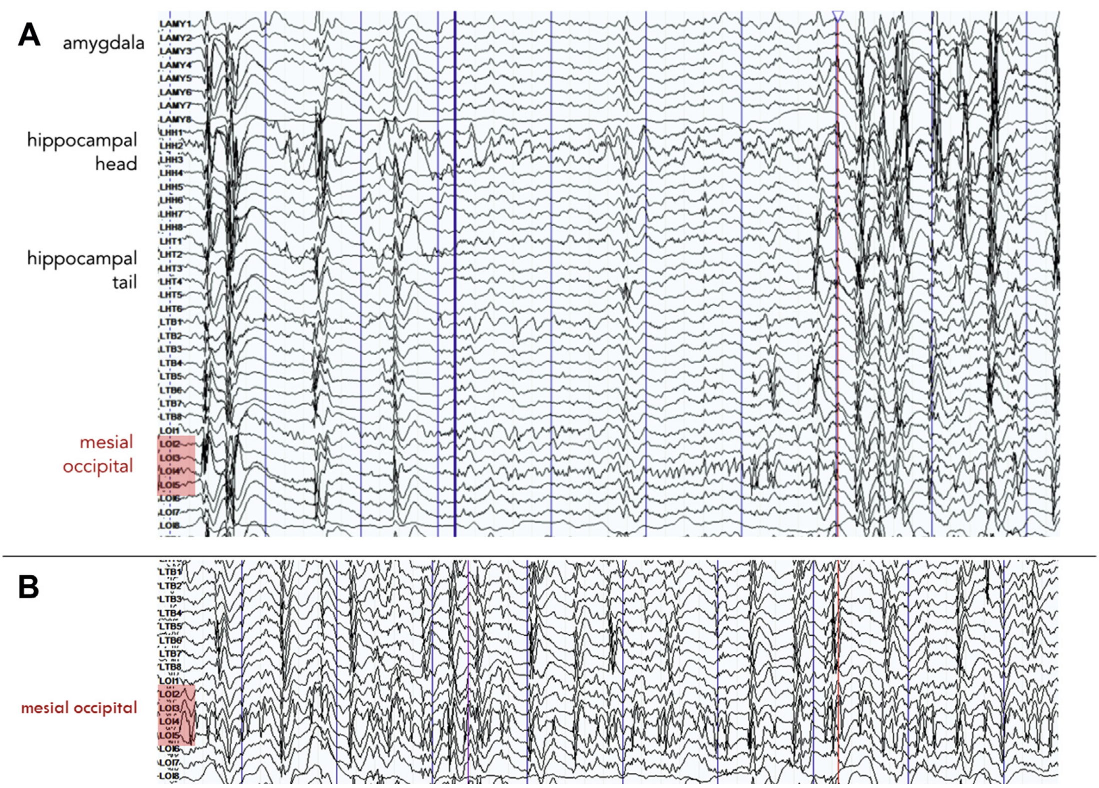

Fig. 4. Case example: seizure 2. Intracranial EEG recording of ictal onset from the mesial-occipital cortex (*A*). (*B*) The sustained seizure in the same contacts (*red boxes* indicate the same mesial-occipital contacts in each panel), a pattern that was not prominent in other recording locations.

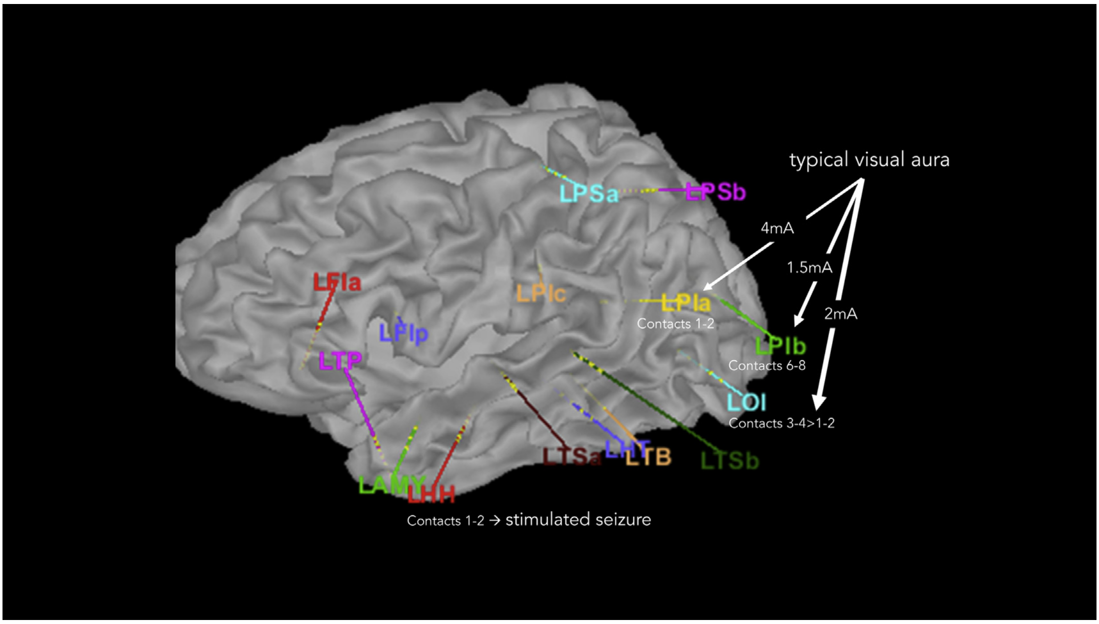

Fig. 5. Case example: seizure 3. Seizure induced by hippocampal stimulation.

network has been optimally characterized. As the patient places his or her trust in the neurosurgeon to safely perform each procedure, we are obligated to assess the data obtained at each stage to the best of our abilities. Inherent in this obligation is the imperative for the epilepsy surgeon to develop an understanding of the current literature related to the interpretation of intracranial EEG, imaging characteristics of potentially epileptogenic lesions, and an ability to read the basic features of EEG, even if this function traditionally is considered the province of our neurology colleagues.

Evolving Concepts in Network Evaluation

Related to this, an important decision point that must be considered in SEEG evaluations regards the use of stimulation to probe the seizure network. Reproducing the usual seizure by low-frequency stimulation is generally accepted to

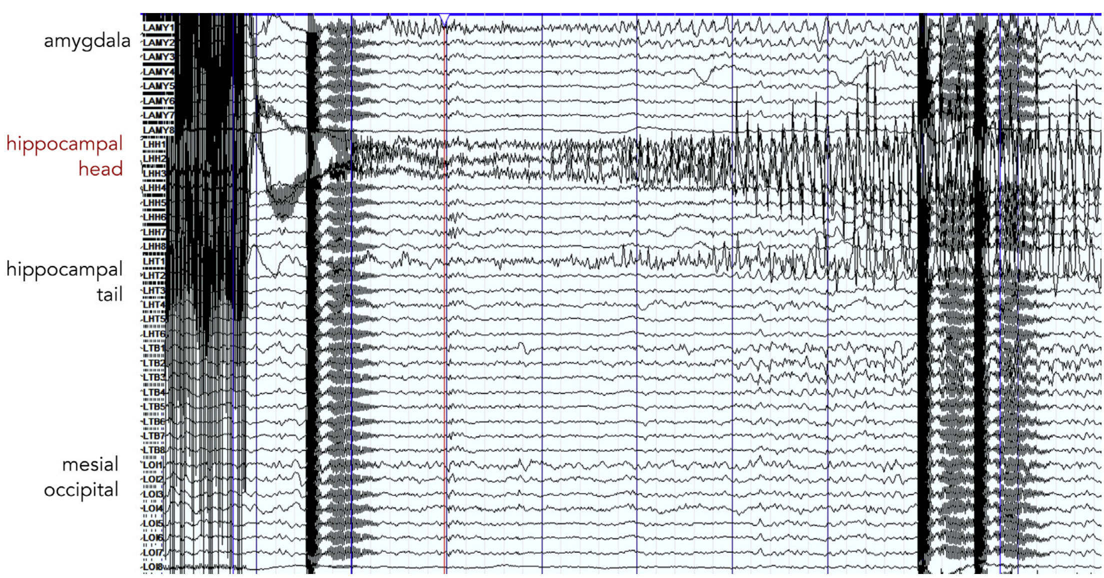

Fig. 6. Case example: stimulation mapping. Reconstruction of electrode implantations and summary of stimulation results.

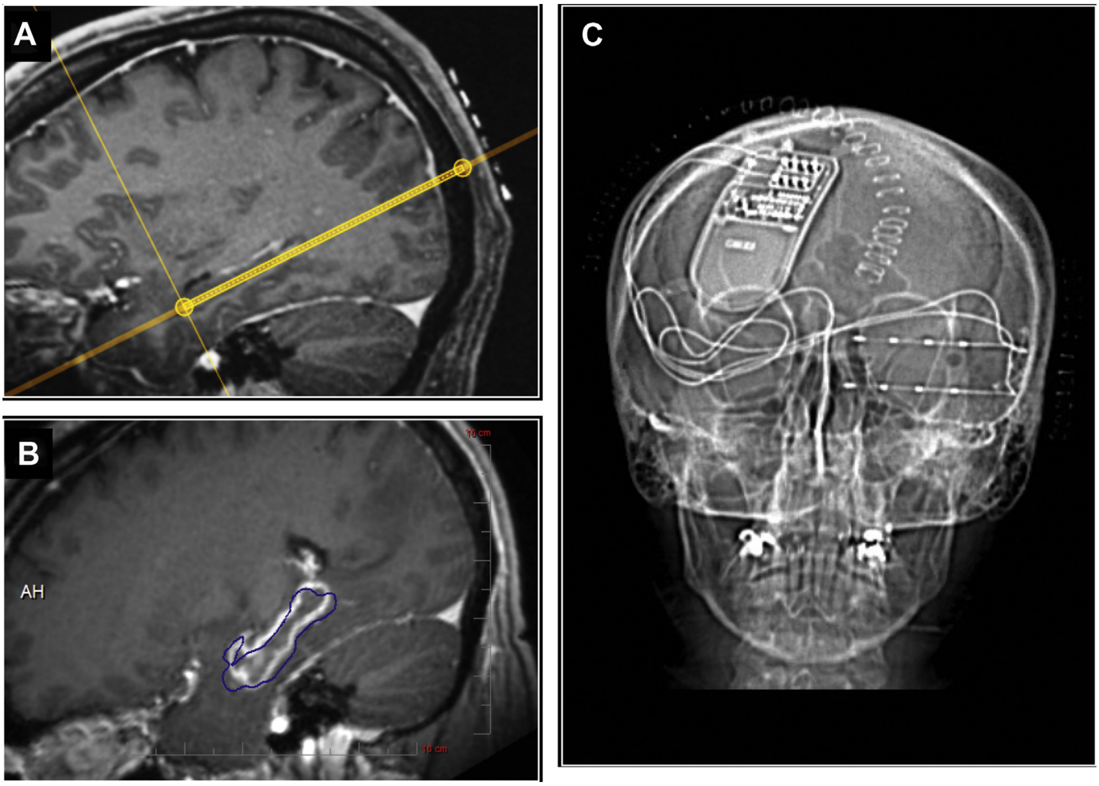

Fig. 7. Case example: combinatorial therapy. The intraoperative-MRI targeting plan for laser thermal ablation (*A*), and 1-month postprocedure imaging with treatment boundaries (*blue*) coregistered to the contrasted MRI, showing the expected treatment-related changes (*B*). Scout image from the postoperative computed tomography scan following RNS implantation with leads targeting the mesial-occipital cortex (*C*).

help define the epileptogenic zone in cases of seizures originating from the hippocampus or from areas of Type 2 focal cortical dysplasia. There is less consensus regarding the interpretation other stimulation strategies. In general, however, clinical signs of the habitual seizure must appear before the propagation of the electrical discharge to the structures connected with the stimulated site to be considered pertinent to defining the epileptogenic zone. Seizures that begin following an afterdischarge, with the recruitment of a local or remote network, are more likely to indicate a false positive. Likewise, high-frequency stimulation is more likely to result in seizures than low-frequency stimulation, including inhabitual seizures, with the intensity of stimulation thought to be indirectly proportional to the significance of the elicited seizure. The use of electrical stimulation to define the epileptogenic zone is not a component of the standard approach at most American epilepsy centers. It seems prudent, nonetheless, to use this tool whenever the epileptogenic zone has not been clearly defined by SEEG recording alone, at the very least.

The preceding concepts relate to the ability of the epilepsy surgeon and team to determine whether the seizure network has been optimally mapped in any given patient. As has been discussed, this is determined by the extent to which the preoperative hypothesis was fully formed, the intracranial monitoring investigation was planned appropriately, and the electroclinical data were carefully analyzed. One factor not yet discussed is how to consider the participation of subcortical structures in generating or maintaining seizures, especially in light of the fact that the target structure for which DBS is approved is the ANT. The limitations of the concept of searching for a cortical epileptogenic focus have been recognized, even in the United States, for more than 60 years. In 1954, Russel Meyers,[11] the functional neurosurgeon and first chair of neurosurgery at the University of Iowa, wrote that the concept of an epileptogenic focus was a “seemingly useful hypothesis, not a proven fact,” in large part because “the results ascribable to the excision of the epileptogenic focus are not greatly impressive.” Remarkable for that time, Meyers[11] published intracranial recordings from the caudate and thalamus of patients with epilepsy and described that "hypersynchronic waves at different regions sometimes appeared temporally related to one another, at other times, wholly independent." Indeed, our best surgical outcomes in the modern era still are achieved by temporal lobectomy, yet at 10 years postoperatively, more than half of these patients are not seizure free on average; the best durability being achieved in patients with hippocampal sclerosis, nearly two-thirds of whom can remain seizure free past 10 years.[12] There are a multitude of potential explanations for this success rate, related to lack of identification or removal of the "seizure focus." In addition, there is Palmini and Paglioli's[13] concept that relevant epileptogenic tissue could be inactive during Phase II evaluations but could exhibit latent manifestation as an epileptogenic zone leading to seizure recurrence. Alternatively, we should explore whether the notion of focal versus nonfocal epilepsy is a false dichotomy, and whether instead it would be beneficial to think of focal, multifocal, diffuse-onset, and idiopathic generalized epilepsies as existing in a continuum of network complexity. In this framework, these types of epilepsy are characterized by the functional-anatomic complexity of their seizure networks. Pathologic activity in the thalamus and basal ganglia may very well have prominent roles in some of these networks. Data supporting this hypothesis exist in functional imaging studies, reports of seizures recorded from the thalamus in patients with idiopathic generalized epilepsy, and reports on the effects of thalamic stimulation for nongeneralized epilepsy.

Should the thalamus be included in diagnostic implantations to characterize certain types of epilepsy? Several centers have begun tackling this important question. The Marseille group reported on a series of 13 patients with temporal lobe epilepsy retrospectively selected based on the presence of an electrode contact residing in the thalamus (electrodes were placed orthogonally for the primary purpose of assaying overlying structures). These recordings demonstrated very early involvement of the thalamus in 4 patients and delayed involvement in 7 patients. Likewise, Pati and colleagues[14] reported data from 11 patients undergoing SEEG for suspected temporal lobe epilepsy, who were implanted in the ANT for research purposes. Temporal changes in ictal power of neural activity within the ANT were observed to be similar to those of the onset zone, and seizure onset was preceded by a decrease in the mean power spectral density in both the thalamus and seizure-onset zone. This group separately reported the early ictal recruitment of the midline thalamus in 3 cases of mesial temporal lobe epilepsy, in which stimulation of either the thalamus or hippocampus induced similar habitual seizures.[15] 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 also recently described by the Birmingham group.[16] Thus, it seems quite reasonable that the implantation of thalamic nuclei may become a valuable component of SEEG strategies to address network hypotheses that prominently feature thalamic involvement.

Off-Label Use of Neuromodulation

Surgical treatment of the network is evolving also to include applying brain stimulation to multifocal and generalized epilepsies, indications that are currently off-label. DBS of the centromedian region of the thalamus improves both the scalp EEG background and the frequency and severity of generalized seizures,[17,18] including in pediatric cases.[19] RNS also has achieved off-label therapeutic success, in pediatrics[20,21] and in generalized epilepsies.[22] We recently reported the first use of bilateral thalamic RNS for idiopathic generalized epilepsy, demonstrating the potential of seizure detection and stimulation in the thalamus to control broad seizure networks.[23] Regarding the decision to recommend neuromodulation for an off-label indication, it is imperative to disclose the experimental nature of the procedure to the patient, along with any biases that may affect the recommendation decision. If the application of closed-loop brain stimulation to multifocal and generalized epilepsies is to become successful, it will require learning how to make the therapy adaptive to any given patient's network characteristics. Personalization of closed-loop brain stimulation will require constant analysis of many complex neurophysiological features in recorded data,[24,25] including the identification of electrophysiological biomarkers of treatment response.[26] Thus, critical decisions in the use of sensing-enabled devices involve deciding how to best monitor and evaluate the recorded data in a timeframe that is consistent with optimizing device management for achieving maximum therapeutic benefit. We must also attain the ability to accurately measure those benefits. In this regard, the field may benefit from the creation of new scales to measure outcomes after surgery on the epilepsy network that prioritize significant changes in patients' quality of life rather than changes in absolute seizure number.

Early Neurosurgical Consultation

As the complexity of surgical therapeutics for epilepsy increases, the surgeon's relationship with the epilepsy team and patient becomes increasingly more important. The concept of early neurosurgical consultation seeks to facilitate this relationship. In this model, rather than referring a patient to the surgeon only on final exhaustion of all noninvasive testing and a subsequent decision that the patient is "ready to talk about surgery," patients are encouraged to meet with an epilepsy surgeon as soon as it is clear they have failed 2 appropriately chosen medications, to discuss the spectrum of potential future role of surgery in the treatment of their disease.[27,28] For instance, the University of Pittsburgh Comprehensive Epilepsy Center adopted a policy termed SAFE, Surgical Approaches For Epilepsy, in which patients with epilepsy likely to be surgical candidates were referred for early neurosurgical consultation, in parallel with their presurgical evaluation. Hearing directly from the person who may perform a surgical intervention for them at some point in the future can alleviate undue anxiety for the patient and lead to more efficient completion of noninvasive studies. The surgeon is provided the benefit of additional opportunities to earn the trust of the patient as well as of the referring epileptologists, through helping to guide the patient through the complex presurgical evaluation.

SUMMARY

Understanding an individual patient's seizures as events that emerge from a dysfunctional brain network is critical for determining how to best optimize a personalized treatment plan. This approach is key to understanding the limitations of current therapies and to recognizing opportunities for surgical innovations that can increase our ability to improve quality of life for patients with epilepsy.

DISCLOSURE

The author has served as a consultant for NeuroPace, Medtronic, and Zimmer Biomet.

REFERENCES

1. Faingold CL. Emergent properties of CNS neuronal networks as targets for pharmacology: application to anticonvulsant drug action. Prog Neurobiol 2004;72:55–85.
2. Mikulecky DC. Complexity, communication between cells, and identifying the functional components of living systems: some observations. Acta Biotheor 1996;44:179–208.
3. Freeman WJ, Kozma R, Werbos PJ. Biocomplexity: adaptive behavior in complex stochastic dynamical systems. Biosystems 2001;59:109–23.
4. Bailey P, Gibbs FA. The surgical treatment of psychomotor epilepsy. J Am Med Assoc 1951;145:365.
5. Kahane P, Landré E, Minotti L, et al. The Bancaud and Talairach view on the epileptogenic zone: a working hypothesis. Epileptic Disord 2006;8(Suppl 2):S16–26.
6. Bonini F, McGonigal A, Trébuchon A, et al. Frontal lobe seizures: from clinical semiology to localization. Epilepsia 2013;55:264–77.
7. Chauvel P, Gonzalez-Martinez J, Bulacio J. Presurgical intracranial investigations in epilepsy surgery. Handb Clin Neurol 2019;161:45–71.
8. Isnard J, Taussig D, Bartolomei F, et al. French guidelines on stereoelectroencephalography (SEEG). Neurophysiol Clin 2018;48:5–13.
9. Tandon N, Tong BA, Friedman ER, et al. Analysis of morbidity and outcomes associated with use of subdural grids vs stereoelectroencephalography in patients with intractable epilepsy. JAMA Neurol 2019;76:672–81.
10. Ma BB, Fields MC, Knowlton RC, et al. Responsive neurostimulation for regional neocortical epilepsy. Epilepsia 2019;61:96–106.
11. Meyers R. The surgical treatment of "focal" epilepsy: an inquiry into current premises, their implementation and the criteria employed in reporting results. Epilepsia 1954;3:9–36.
12. Hemb M, Palmini A, Paglioli E, et al. An 18-year follow-up of seizure outcome after surgery for temporal lobe epilepsy and hippocampal sclerosis. J Neurol Neurosurg Psychiatry 2013;84:800–5.
13. Palmini A, Paglioli E. Invasive studies of the human epileptic brain. Oxford: Oxford University Press; 2018. p. 120–30. https://doi.org/10.1093/med/9780198714668.003.0010.
14. Pizarro D, Ilyas A, Chaitanya G, et al. Spectral organization of focal seizures within the thalamotemporal network. Ann Clin Transl Neurol 2019;6:1836–48.
15. Romeo A, Roach Alexandra TI, Toth E, et al. Early ictal recruitment of midline thalamus in mesial temporal lobe epilepsy. Ann Clin Transl Neurol 2019;6:1552–8.
16. Chaitanya G, Romeo AK, Ilyas A, et al. Implantation technique, safety and complications of robot-assisted stereoelectroencephalography exploration of the limbic thalamus in human focal epilepsy. Biorxiv 2020. https://doi.org/10.1101/2020.01.27.922195.
17. Valentín A, Navarrete E, Chelvarajah R, et al. Deep brain stimulation of the centromedian thalamic nucleus for the treatment of generalized and frontal epilepsies. Epilepsia 2013;54:1823–33.
18. Martín-López D, Jiménez-Jiménez D, Cabañés-Martínez L, et al. The role of thalamus versus cortex

in epilepsy: evidence from human ictal centromedian recordings in patients assessed for deep brain stimulation. Int J Neural Syst 2016;27:1750010.

19. Sa M, Singh R, Pujar S, et al. Centromedian thalamic nuclei deep brain stimulation and Anakinra treatment for FIRES – Two different outcomes. Eur J Paediatr Neurol 2019. https://doi.org/10.1016/j.ejpn.2019.08.001.
20. Singhal NS, Numis AL, Lee MB, et al. Responsive neurostimulation for treatment of pediatric drug-resistant epilepsy. Epilepsy Behav Case Rep 2018; 10:21–4.
21. Kokoszka MA, Panov F, Vega-Talbott ML, et al. Treatment of medically refractory seizures with responsive neurostimulation: 2 pediatric cases. J Neurosurg Pediatr 2018;21:421–7.
22. Herlopian A, Cash SS, Eskandar EM, et al. Responsive neurostimulation targeting anterior thalamic nucleus in generalized epilepsy. Ann Clin Transl Neurol 2019;6:2104–9.
23. Kokkinos V, Urban A, Sisterson ND, et al. Responsive neurostimulation of the thalamus improves seizure control in idiopathic generalized epilepsy: a case report. Neurosurgery 2020. https://doi.org/10.1093/neuros/nyaa001.
24. Sisterson ND, Wozny TA, Kokkinos V, et al. A rational approach to understanding and evaluating responsive neurostimulation. Neuroinformatics 2020;1–11. https://doi.org/10.1007/s12021-019-09446-7.
25. Sisterson ND, Wozny TA, Kokkinos V, et al. Closed-loop brain stimulation for drug-resistant epilepsy: towards an evidence-based approach to personalized medicine. Neurotherapeutics 2018. https://doi.org/10.1007/s13311-018-00682-4.
26. Kokkinos V, Sisterson ND, Wozny TA, et al. Association of closed-loop brain stimulation neurophysiological features with seizure control among patients with focal epilepsy. JAMA Neurol 2019; 76:800–8.
27. Kwan P, Arzimanoglou A, Berg AT, et al. Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. Epilepsia 2010;51:1069–77.
28. Sugano H, Arai H. Epilepsy surgery for pediatric epilepsy: optimal timing of surgical intervention. Neurol Med Chir 2015;55:399–406.