

Personalizing Responsive Neurostimulation for Epilepsy

Vikram R. Rao

Department of Neurology and Weill Institute for Neurosciences, University of California, San Francisco, San Francisco, California, U.S.A.

Summary: Over the past 20 years, responsive neurostimulation (RNS), a closed-loop device for treating certain forms of drug-resistant focal epilepsy, has become ensconced in the epileptologist's therapeutic armamentarium. Through neuromodulatory effects, RNS therapy gradually reduces seizures over years, providing diagnostically valuable intracranial recordings along the way. However, the neuromodulatory potential of RNS therapy has not been fully harnessed. Seizure reduction is often slow, outcomes vary across individuals and defy prognostication, seizure freedom is uncommon, and many patients do not derive significant benefit. These limitations may stem from the "black box" nature of RNS therapy. The antiseizure mechanism(s) of RNS remain poorly understood, and, in the absence of first principles to inform selection of the candidates most likely to benefit, the ideal brain regions to

target, and the most effective stimulation parameters, contemporary use of RNS therapy is largely empiric. Fortunately, recent advances in neuroimaging, neurophysiology, artificial intelligence, and engineering have made the goal of rational, personalized neurostimulation a near-term reality. Here, we review recent progress toward this goal, focusing on novel approaches to patient selection, brain network topology, state-dependent effects, and stimulation parameter optimization. By considering the who, where, when, and how of RNS, we highlight emerging paradigm shifts that will help usher in a new age of RNS therapy that is more personalized and more effective.

Key Words: RNS, Closed-loop, Seizure, Drug-resistant epilepsy, Neuromodulation, Brain networks.

(J Clin Neurophysiol 2025;42: 505–512)

Epilepsy is a common neurologic disorder afflicting one in 26 people during their lives and nearly 50 million people worldwide.^{1,2} The hallmark of epilepsy is recurrent seizures, bouts of excessive electrical activity that arise from dysfunctional brain networks and cause significant morbidity and mortality. Over 30 antiseizure medications (ASMs) are available,³ but one-third of people living with epilepsy—including over 1.5 million people in the United States⁴—still have uncontrolled seizures. Surgical resection of seizure-producing brain tissue is potentially curative but not always feasible, so responsive neurostimulation (RNS) has emerged as a promising alternative.^{5–7} The RNS System comprises a cranially implanted pulse generator and two intracranial lead wires that deliver electrical stimulation directly to the seizure focus/foci in the brain. In a closed-loop design, the RNS device continuously senses neural activity and stimulates the brain only upon detection of abnormal patterns that may herald seizures.⁸ Originally conceived to terminate incipient seizures akin to a cardiac defibrillator, the primary mechanism of seizure reduction with RNS therapy is now believed to be neuromodulatory,^{9–11} i.e., progressive dampening of hyperexcitable neural circuits over months to years.

Despite these emerging mechanistic insights, the neuromodulatory potential of RNS therapy has not been fully harnessed. Seizure reduction can take years, seizure freedom is rare, and over a quarter of patients are nonresponders (<50% reduction in seizure frequency).¹² A principal barrier to accelerating and improving outcomes with RNS is the "black box"

nature of the therapy. Over 12 million combinations of stimulation waveform parameters (current intensity, frequency, etc.) are possible,¹³ but there are no established biomarkers to guide selection of the optimal combination(s) for a given patient. As a result, the contemporary approach to RNS programming involves an empiric process of trial-and-error. Standard stimulation settings adapted from clinical trials are initially applied to all patients and thereafter iteratively adjusted without biomarker guidance every few months, a "one-size-fits-all" approach that belies the heterogeneity of epilepsy and underscores a stark reality: Twenty years after the advent of RNS, clinicians still navigate a vast stimulation parameter space in the dark, and patients still suffer from seizures while waiting to chance upon effective settings. Indeed, long-term clinical trials¹² and real-world outcome studies¹⁴ have cemented a place for RNS therapy in the epileptologist's armamentarium, but, with nearly 7,000 drug-resistant patients now treated with RNS in the United States, several limitations of this therapy have also become clear.

1. Median reductions in seizure frequency reported in clinical trials of RNS obscure the considerable variability in outcomes across individuals, and there are no established means of prognosticating treatment response. Practically, this means that patients must opt for an invasive intracranial device without knowing the extent to which they will benefit, if at all. Given the availability of two other FDA-approved neurostimulation devices (vagus nerve stimulation; deep brain stimulation, DBS) that are conceptually and mechanistically distinct and that may have efficacy comparable to RNS,^{6,15–17} selecting the best device for a given patient remains a challenge.
2. The flexible nature of RNS—including myriad lead configurations and vast stimulation parameter space—enables therapy customization, but rational selection of "optimal"

V. R. Rao serves on the Medical Advisory Board for NeuroPace, Inc., manufacturer of the RNS® System, but declares no targeted funding for this work.

Address correspondence and reprint requests to Vikram R. Rao, MD, PhD, UCSF Epilepsy Center, 400 Parnassus Ave, 8th Floor, San Francisco, CA 94143, U.S.A.; e-mail: vikram.rao@ucsf.edu.

Copyright © 2025 by the American Clinical Neurophysiology Society
ISSN: 1537-1603/25/4206-0505
DOI 10.1097/WNP.0000000000001179

parameters remains elusive because the input/output relationship for brain stimulation is not well-defined. Without knowledge of which location(s) to target or when and how to stimulate, contemporary use of RNS therapy remains largely a guessing game.

3. Chronic electrocorticography data provided by RNS is one of its biggest advantages over other devices,^{18–21} although DBS also provides certain forms of long-term neurophysiology.²² Over 20 million RNS electrocorticograms (ECoGs) have been stored to date, but “big data” poses a challenge for clinicians tasked with reviewing, interpreting, and leveraging these recordings for patient’s benefit. Potential applications of chronic RNS data have been extensively reviewed¹⁸ and include characterizing the relationship between electrographic and patient-reported events^{23–25}; quantifying seizure dynamics^{26–29}; gauging effects of ASMs^{30–32}; forecasting seizures^{33–38}; determining neural correlates of patient behavior^{39,40} or epilepsy procedures^{41–43}; serving as a platform technology for neuroscience research^{44,45}; and enabling circuit-based treatment of neuropsychiatric disease.^{46–50} Automated tools to help clinicians distill clinically salient, patient-specific insights from voluminous data are sorely needed.
4. RNS is considered among the most advanced medical devices, yet its technology is outdated. The first patient was treated over 20 years ago. The current second-generation device (Model RNS-320), which brought improvements over its predecessor (RNS-300M) in memory capacity, battery life, and magnetic resonance imaging compatibility, cannot keep step with the blistering pace of advances in engineering and computational power because of the slow process of medical device regulatory approval. For example, onboard memory remains extremely limited (~48 channel-minutes of ECoG sampled at 250 Hz), data transfer to a secure online repository (Patient Data Management System) is neither automatic nor continuous, seizure detection tools (based on calculations of signal line length, half-waves, or area under the curve) are computationally efficient but have limited flexibility, alerts are not provided, and, currently, the device cannot be programmed remotely. Critically, although the device is responsive to brain activity, it is not adaptive to the momentary state of brain networks; in other words, the device behaves the same way between programming sessions, typically separated by months, although brain states are highly dynamic in the interim.^{51–53}

The collective impact of these limitations is that it is likely that at least some patients treated with RNS could be doing better than they are now. Still, first principles remain elusive, and clinicians who use RNS can easily succumb to a sort of “neurostimulation nihilism,” a view that the “rules” are unknowable and that virtually any empiric approach to RNS therapy will benefit most patients and not benefit some. Are we left then to simply deliver electrons to the brain, cross our fingers, and hope for the best? The purpose of this article is to argue against the defeatist mindset and in favor of a view that rational, personalized neurostimulation is a near-term reality. Recent advances in neuroimaging, neurophysiology, artificial intelligence (AI), and engineering have brought us closer than ever to the goal of

optimizing neurostimulation outcomes in all patients. Here, we review recent progress toward this goal, focusing on the who, where, when, and how of brain-responsive neurostimulation (Fig. 1).

WHO TO STIMULATE—PATIENT SELECTION

The large RNS stimulation parameter space, encompassing all possible stimulation waveforms, lead placements, and anode/cathode designations for electrodes,⁵⁴ is a mixed blessing: clinicians always have something new to try, but, for patients who are not responding well to RNS therapy, hope for a better outcome can fade long before all options are exhausted. Anecdotally, although electrographic evidence of treatment response often manifests within the first 6 months of therapy,⁵⁵ significant clinical improvement can be observed even 2 or more years into the course of treatment. Ideally, the likelihood of treatment response in an individual could be estimated before invasive device implantation. Progress has been made in this regard, predicated on the notion that some brain networks may be intrinsically more “susceptible” to RNS stimulation than others. Retrospective analysis of seizures recorded during intracranial electroencephalography in patients who went on to receive RNS revealed that ictal synchronizability, which reflects the ease by which neural activity propagates through a functionally connected brain network, is inversely related to the extent of seizure reduction with RNS therapy.¹¹ Although not yet prospectively validated, this suggests a means by which RNS responders and nonresponders can be distinguished before device implantation based on electrographic features of their seizures. Another recent study using pre-RNS interictal magnetoencephalography found that frequency-specific global functional connectivity was higher in RNS responders compared with nonresponders.^{56,57} Similarly, theta frequency connectivity between the anterior nucleus of the thalamus and scalp EEG is stronger in responders to thalamic DBS⁵⁸ than in nonresponders. Taken together, a picture is emerging that efficacy of neurostimulation depends both on intrinsic properties of seizures and the brain networks that give rise to them. A speculative possibility is that RNS stimulation can more readily diffuse through networks with high functional connectivity, potentiating its therapeutic effects, and that seizures less able to synchronize widespread networks are those most readily mitigated by RNS stimulation.

An alternative approach to optimizing the efficacy of neurostimulation on a per-patient basis has been developed in the context of chronic subthreshold cortical stimulation, which involves an open-loop device that delivers continuous electrical stimulation to the seizure onset zone (SOZ).⁵⁹ During intracranial monitoring, a trial of electrical stimulation is applied to the SOZ and surrounding electrodes while monitoring the EEG for frequency-specific changes in spectral power and reduction in interictal epileptiform activity (IEA).^{60,61} The results can help guide stimulation location and parameter choice before permanent device implantation for chronic subthreshold cortical stimulation. Conceivably, a similar approach could be taken in patients undergoing, for example, stereotactic EEG before RNS implantation.^{62,63}

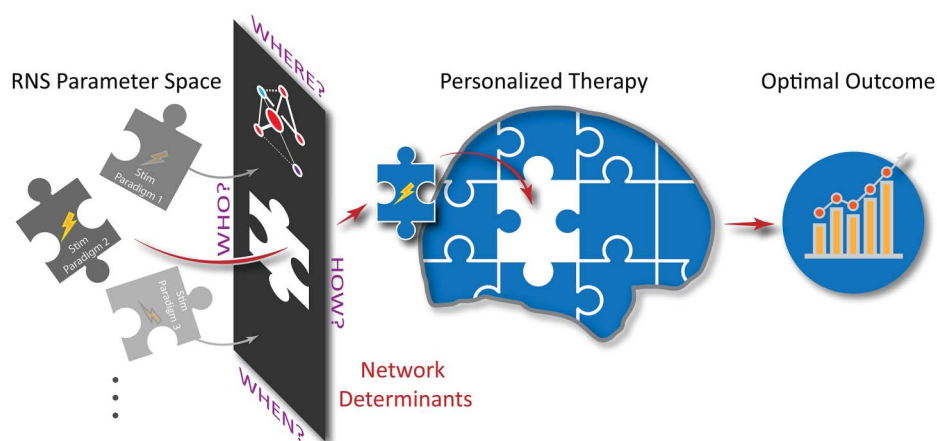


FIG. 1. Personalizing RNS therapy. The RNS stimulation (“Stim”) parameter space is vast, but brain network determinants of who, where, when, and how to stimulate may enable personalized selection of a stimulation paradigm that yields optimal clinical outcome.

Traditionally reserved for delineating cortical regions for resection or ablation, stereotactic EEG in contemporary practice is increasingly used to sample subcortical components of the epileptic network, especially thalamic nuclei.⁶⁴ Although this remains controversial, the growing experience with thalamic stereotactic EEG has revealed that seizures reliably involve specific thalamic nuclei in circuits connected to the SOZ.^{65–67} However, it does not necessarily follow that stimulating these nuclei will have a therapeutic effect, nor is it clear that lack of ictal involvement in a thalamic nucleus means that stimulation there will be ineffective.⁶⁸ Still, preliminary evidence indicates that thalamic stimulation can induce changes in effective thalamocortical connectivity,⁶⁹ suggesting a personalized preimplant biomarker for assessing the extent of network plasticity that may be possible with a neurostimulation device.

WHERE TO STIMULATE—CRITICAL NETWORK NODES

RNS was designed to terminate seizures soon after their onset, so, intuitively, stimulating electrodes are traditionally placed as close as possible to the SOZ. As our understanding of the mechanism(s) by which RNS reduces seizures continues to evolve, it is worth noting the paucity of evidence supporting this lead placement strategy. Indeed, several studies of hippocampal neurostimulation have failed to find a clear link between the precise anatomical location of electrodes and patient outcomes.^{70–72} However, outcomes can be predicted with information about the specific brain circuit(s) being stimulated. For example, in a study of patients with RNS with hippocampal electrodes, seizure reduction was greatest when diffusion imaging revealed that the volume of tissue activated shared structural connectivity with other regions in the default mode network, including medial prefrontal cortex, cingulate cortex, and precuneus.⁷¹ Since subfields of the hippocampus have differential connectivity to cortical regions in the default mode network,⁷³ this suggests that the current strategy of placing RNS leads based on anatomic landmarks should be expanded to include consideration of patient-specific networks.

The network theory of epilepsy,⁷⁴ now firmly entrenched in the field, steadily gained credence in parallel with the rise of modern approaches to neurostimulation, perhaps explaining the shift from trying to suppress the seizure “focus” to modulating the dysfunctional circuits that give rise to seizures.⁷⁵ Brain networks have nodes where targeted stimulation can exert high influence over distributed activity.^{76,77} Conceptually, seizure-producing networks may have a point(s) of vulnerability—a neurophysiologic Achilles’ heel—where electrical stimulation is particularly effective. Some have even proposed extension of the classical zones of Lüders⁷⁸ to include “neuromodulation zones,” areas where stimulation produces clinically meaningful seizure reduction,⁷⁹ which may or may not colocalize with the SOZ. Defining network targets for stimulation may involve anatomic subregions of brain structures,^{80,81} structural connectivity,⁷¹ functional connectivity (i.e., so-called “projection” vs. “receiver” nodes⁸²), electrophysiologic signatures like fast ripples,⁸³ or the confluence of key white matter tracts.⁸⁴ Work in animal models of epilepsy suggests that responsive stimulation applied at different targets concurrently can have synergistic effects.⁸⁵ Multisite stimulation in humans is possible with existing devices^{86,87} and may become increasingly feasible as new devices with more than two leads become available in the future. Finally, using structural and functional connectivity to predict network sites of greatest stimulation-induced plasticity may enable identification of the optimal stimulation target.⁸⁸

The question of where to stimulate is particularly relevant for the thalamus, which, from a graph theory perspective, has the highest connectivity of any node in the seizure network because of its extensive inputs and outputs.⁸⁹ Indeed, the recent explosion of interest in stimulating the thalamus⁹⁰ relates to the fact that this central hub has such diverse circuit topologies. After anterior nucleus of the thalamus, which was studied in clinical trials of thalamic DBS,⁹¹ the centromedian nucleus is arguably the most common thalamic neurostimulation target, as it has been targeted for focal and multifocal epilepsy^{92–95} as well as generalized epilepsy,^{92,96–98} although the pulvinar is gaining ground.^{99–104} As discussed above, thalamic stereotactic EEG may help personalize selection of a thalamic nucleus for neuromodulation.⁶³ Although there is currently no established rubric for targeting a specific thalamic nucleus based on the location of the

SOZ, an emerging strategy involves thalamocortical hodology, the study of structural and functional connectivity between thalamus and overlying cortex.¹⁰⁵ The concept of hodological matching—i.e., optimal seizure reduction is achieved by stimulating the thalamic nucleus whose connectivity best aligns with the location of the cortical SOZ¹⁰⁵—is intellectually appealing but will require more clinical validation.

WHEN TO STIMULATE—STATE-DEPENDENT EFFECTS

The brain is never truly at rest, and brain stimulation paradigms intended to manipulate brain activity need to account for fluctuating states. For example, states of consciousness can significantly alter the way in which stimulation-induced neural activity spreads over long-range connections.¹⁰⁶ Stimulation-induced modulation of memory performance¹⁰⁷ and mood¹⁰⁸ depends on the momentary state of the brain, and DBS for treatment of essential tremor is effective when timed to specific phases of the pathologic movement that are underpinned by oscillations of neural circuits.¹⁰⁹ Therefore, state-dependent brain stimulation¹¹⁰ for epilepsy makes intuitive sense, and the neuronal biophysical correlates of this concept are being unraveled.¹¹¹ Opportunities with state-dependent stimulation include potentially more effective seizure reduction and greater tolerability. For example, switching stimulation frequency at night¹¹² can help avoid the sleep-disrupting effects of thalamic stimulation.¹¹³ However, RNS in its present form is sensitive to brain state only indirectly through detection of seizures and interictal epileptiform activity. By using these detections to infer changes in underlying brain state, recent studies have revealed that RNS stimulation parameters that are effective in one state may be ineffective—or even counterproductive—when the brain transitions to a different state.^{52,114} For example, it has been proposed that RNS stimulation delivered during brain states with less IEA facilitates long-term seizure reduction.¹¹⁵

Although the RNS neurostimulator does not store continuous ECoG, hourly counts of device-detected IEA are stored for up to 28 days. Mathematical analyses that extract cyclical patterns from time series¹¹⁶ have revealed that, in addition to ubiquitous daily (circadian) cycles,^{117,118} multiday (multidien) cycles of IEA are present in most individuals with RNS (~60%¹¹⁷), tend to be stable over time,^{35,119} and may reflect disease activity.³⁰ Critically, patient-reported and electrographic seizures preferentially occur on the rising phases of multidien IEA cycles.^{35,120} A phasic relationship between seizures and IEA, also observed for circadian cycles,¹²¹ is remarkably conserved across species.¹²² The revelation that seizures are not as random as once thought,¹¹⁹ and that IEA cycle phase determines seizure risk state, enables a strategy for estimating the likelihood of seizure occurrence over future horizons (termed, “seizure forecasting”^{34,123}). More recently, other neurophysiologic features have been found to demonstrate cyclical behavior. For example, analyses of interictal RNS ECoGs recorded from hippocampus revealed cycles of orchestrated, frequency-dependent changes in FC that fluctuate in concert with IEA cycles and can also be leveraged to forecast electrographic

seizures.³³ Other resting-state EEG background features also fluctuate in concert with IEA cycles,⁵¹ including the aperiodic component of neural activity.^{71,124} Mounting evidence indicates that cycles in epilepsy are relevant for therapeutic neurostimulation: circadian modulation of aperiodic activity is a putative early biomarker of response to RNS therapy¹²⁵; thalamic DBS can modulate IEA cycles¹²⁶; and the relationship between IEA cycles and EEG features is attenuated after neurostimulation.⁵¹ Combinations of EEG features like aperiodic activity and IEA cycle amplitude/phase have potential to provide practical biomarkers of disease state⁴¹ and RNS treatment response,¹²⁷ but whether these will be patient-specific or generalizable remains to be seen.

Leveraging neurophysiologic features that reflect brain state requires a device that can sense the relevant biomarker. For example, the current version of the RNS neurostimulator cannot directly detect functional connectivity, aperiodic activity, or IEA cycle phase. However, platforms are being developed to improve parameterization of RNS detectors for specific neurophysiologic states of seizure networks.^{128,129} Encouraged by the recent success of adaptive DBS for Parkinson disease,¹³⁰ next-generation closed-loop neurostimulation devices for epilepsy will be sensitive to the state of the brain network.¹³¹ Hardware and software advances, including neuromorphic computing¹³² and multiplex-then-amplify schemes,¹³³ are increasingly enabling on-chip analysis of neural signals and real-time, AI-driven¹³⁴ stimulation optimization.¹³²

HOW TO STIMULATE—PARAMETER SPACE NAVIGATION

Until next-generation devices become available to “neurostimulationists” in an AI-augmented future,¹³ clinicians must continue to program RNS devices by making the most of the information at hand. Designed as a seizure-terminating device, RNS has hyperacute effects on neural activity,^{51,135,136} but acute seizure disruption is not the only mechanism of action for RNS,¹³⁷ and most of its seizure-reducing effects unfold over much longer timescales.^{9,12,55,138} However, clinicians need rapid, quantifiable feedback to inform decision making during in-person device programming sessions. One challenge relates to efficiently reviewing and interpreting electrocorticography data stored by the RNS neurostimulator to plan adjustments to detection, stimulation, and storage settings.¹³⁹ Deep learning neural networks can detect seizures in RNS ECoGs with high accuracy,^{140–142} so this task will likely be automated for clinicians soon. For patients who are not responding optimally to RNS therapy, deep learning models can also identify other patients with similar ECoG features but better clinical outcomes, which may facilitate selection of more effective stimulation settings¹⁴³; essentially, the rationale is that what worked for one patient may work for another patient with similar neurophysiologic characteristics.

In the era of big data in epilepsy,¹⁴⁴ AI-based tools are well-suited to reverse engineer input/output relationships and distill the vast stimulation parameter space into a manageable set of programming variables to achieve personalized clinical

goals.^{13,134} Fortunately, brain responses to neurostimulation have been shown to be constrained by functional connectivity and neuroanatomy, and large dataset mapping of input/output relationships across individuals has revealed a limited repertoire of responses to diverse stimulation parameters. Since brain responses are constrained by amalgamated structural/functional networks, it may not be necessary to test every possible combination of stimulation parameters.¹³ Instead, seemingly infinite stimulation parameter combinations are funneled by the brain into a limited number of predictable responses. A general atlas of these responses¹⁴⁵ would help navigate and narrow the vast parameter space, making feasible the dream of rational programming to achieve a desired outcome.¹³

Epilepsy is a test case for many other neuropsychiatric conditions that are symptomatic of network dysfunction and that would be amenable to personalized, closed-loop brain stimulation.^{146,147} Conceptually, the challenge is to find the balance between standardization (i.e., the limited array of physiologic outputs in relation to innumerable possible stimulation inputs) and personalization (i.e., patient-specific constraints related to brain structural and functional connectivity).¹³ By analogy, although the possible materials and designs for making shoes are seemingly infinite, most shoes can be binned into a limited number of categories. So, when shoes are needed, it is not necessary to start from scratch with every conceivable means of creating a foot covering; only the intended application needs to be known, and the initially selected template can be refined by choosing the desired color, size, insoles, laces, etc. Will personalized neurostimulation for epilepsy ever evolve such practical simplicity? If the shoe fits...

CONCLUSION

In what seems a distant memory now, the first incarnation of RNS was a battery-operated external desktop device electroencephalogram, and its ability to terminate seizures was evaluated in four patients undergoing intracranial monitoring with subdural electrodes. In this preliminary study, Kossoff and colleagues made several prescient observations¹⁴⁸:

In patient 3, an apparent clinical effect was not seen until stimulation parameters were modified, perhaps indicating that stimulation parameters require individual adjustment. Interestingly, in the fourth patient, the subdural EEG recordings appeared to normalize after several days of stimulation, suggesting a possible neuromodulatory effect of this repetitive direct brain stimulation. In addition, patient 1 seemed to have had electrographic change even though the current may not have been directly over the epileptogenic cortex.

Thus, from its earliest use, RNS therapy has been known to have different effects in different individuals, to require personalized tuning of stimulation parameters and time for neuromodulatory effects to unfold, and to have indirect network-based effects remote to the site of stimulation. For the past 20 years, personalization of RNS therapy has meant tailoring detection settings on the device for early and specific

detection of each patient's unique ictal pattern. This makes sense only to the extent that the therapeutic mechanism involves acute seizure termination. In the next 20 years, it seems likely that personalization will increasingly involve features of the interictal state: resting-state neural biomarkers that inform lead optimal placement and enable reliable outcome prognostication; brain state dynamics between seizures; cyclical patterns of epileptiform activity; and network responses to stimulation applied outside of seizures. Therapy optimization based on these and other biomarkers will likely be facilitated by engineering advances. A next-generation RNS device could potentially include more than two leads; higher sampling rate; larger data storage capacity; on-device AI; seamless data streaming; integration with wearable, handheld, and other implanted devices; and the ability to provide seizure alerts.

The emerging view is that the efficacy of RNS may depend less on aborting seizures that have already started and more on modulating patient-specific networks to prevent seizures from starting in the first place. More work is needed because, despite enormous advances in our understanding of the mechanism of RNS and ways to personalize this therapy, fundamental questions remain. If the rapid pace of recent discoveries in this field is any guide, although, the community of clinicians and people living with epilepsy will not have to wait another 20 years for the answers.

ACKNOWLEDGMENTS

The author is grateful to the Ernest Gallo Foundation for support through an endowed professorship.

REFERENCES

- England MJ, Liverman CT, Schultz AM, Strawbridge LM. Epilepsy across the spectrum: promoting health and understanding. A summary of the Institute of Medicine report. *Epilepsy Behav* 2012;25:266–276.
- GBD 2019 Mental Disorders Collaborators. Global, regional, and national burden of 12 mental disorders in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet Psychiatry* 2022;9:137–150.
- Löscher W, Klein P. The pharmacology and clinical efficacy of antiseizure medications: from bromide salts to cenobamate and beyond. *CNS Drugs* 2021;35:935–963.
- Kobau R, Luncheon C, Greenlund KJ. About 1.5 million community-dwelling US adults with active epilepsy reported uncontrolled seizures in the past 12 months, and seizure control varied by annual family income-National Health Interview Survey, United States 2021 and 2022. *Epilepsy Behav* 2024;157:109852.
- Lundstrom BN, Osman GM, Starnes K, Gregg NM, Simpson HD. Emerging approaches in neurostimulation for epilepsy. *Curr Opin Neurol* 2023;36:69–76.
- Simpson HD, Schulze-Bonhage A, Cascino GD, et al. Practical considerations in epilepsy neurostimulation. *Epilepsia* 2022;63:2445–2460.
- Boddeti U, McAfee D, Khan A, Bachani M, Ksendzovsky A. Responsive neurostimulation for seizure control: current status and future directions. *Biomedicine* 2022;10:2677.
- Jarosiewicz B, Morrell M. The RNS System: brain-responsive neurostimulation for the treatment of epilepsy. *Expert Rev Med Devices* 2021;18:129–138.
- Rao VR, Rolston JD. Unearthing the mechanisms of responsive neurostimulation for epilepsy. *Commun Med (Lond)* 2023;3:166.

10. Foutz TJ, Wong M. Brain stimulation treatments in epilepsy: basic mechanisms and clinical advances. *Biomed J* 2022;45:27–37.
11. Scheid BH, Bernabei JM, Khambhati AN, et al. Intracranial electroencephalographic biomarker predicts effective responsive neurostimulation for epilepsy prior to treatment. *Epilepsia* 2022;63:652–662.
12. Nair DR, Laxer KD, Weber PB, et al. Nine-year prospective efficacy and safety of brain-responsive neurostimulation for focal epilepsy. *Neurology* 2020;95:e1244–e1256.
13. Hadar PN, Zelman R, Salami P, Cash SS, Paulk AC. The Neurostimulationist will see you now: prescribing direct electrical stimulation therapies for the human brain in epilepsy and beyond. *Front Hum Neurosci* 2024;18:1439541.
14. Razavi B, Rao VR, Lin C, et al. Real-world experience with direct brain-responsive neurostimulation for focal onset seizures. *Epilepsia* 2020;61:1749–1757.
15. Li Q, Shan Y, Wei P, Zhao G. The comparison of DBS and RNS for adult drug-resistant epilepsy: a systematic review and meta-analysis. *Front Hum Neurosci* 2024;18:1429223.
16. Alcalá-Zermeno JL, Gregg NM, Starnes K, et al. Invasive neuro-modulation for epilepsy: comparison of multiple approaches from a single center. *Epilepsy Behav* 2022;137:108951.
17. Yang JC, Bullinger KL, Dickey AS, et al. Anterior nucleus of the thalamus deep brain stimulation vs temporal lobe responsive neurostimulation for temporal lobe epilepsy. *Epilepsia* 2022;63:2290–2300.
18. Rao VR. Chronic electroencephalography in epilepsy with a responsive neurostimulation device: current status and future prospects. *Expert Rev Med Devices* 2021;18:1093–1105.
19. Khambhati AN. Utility of chronic intracranial electroencephalography in responsive neurostimulation therapy. *Neurosurg Clin N Am* 2024;35:125–133.
20. Traner CB, King-Stephens D. Insights from chronic ECoG by RNS. *J Clin Neurophysiol* 2024;41:195–199.
21. Rehman M, Higdon LM, Sperling MR. Long-term home EEG recording: wearable and implantable devices. *J Clin Neurophysiol* 2024;41:200–206.
22. Goyal A, Goetz S, Stanslaski S, et al. The development of an implantable deep brain stimulation device with simultaneous chronic electrophysiological recording and stimulation in humans. *Biosens Bioelectron* 2021;176:112888.
23. Karakas C, Ward R, Hegazy M, Skrehot H, Haneef Z. Seizure control during the COVID-19 pandemic: correlating Responsive Neurostimulation System data with patient reports. *Clin Neurophysiol* 2022;139:106–113.
24. Quigg M, Skarpaas TL, Spencer DC, Fountain NB, Jarosiewicz B, Morrell MJ. Electroencephalographic events from long-term ambulatory brain recordings can potentially supplement seizure diaries. *Epilepsy Res* 2020;161:106302.
25. Issa Roach AT, Chaitanya G, Riley KO, Muhlhofer W, Pati S. Optimizing therapies for neurobehavioral comorbidities of epilepsy using chronic ambulatory electrocorticography. *Epilepsy Behav* 2020;102:106814.
26. Chiang S, Fan JM, Rao VR. Bilateral temporal lobe epilepsy: how many seizures are required in chronic ambulatory electrocorticography to estimate the laterality ratio? *Epilepsia* 2022;63:199–208.
27. Arain AM, Mirro EA, Brown D, et al. Long-term intracranial EEG lateralization of epileptogenicity in patients with confirmed or suspected bilateral mesial temporal lobe onsets during epilepsy surgical evaluation. *J Clin Neurophysiol* 2023;41:522–529.
28. Abdulrazeq HF, Kimata AR, Shao B, et al. Laser amygdalohippocampotomy reduces contralateral hippocampal sub-clinical activity in bitemporal epilepsy: a case illustration of responsive neurostimulator ambulatory recordings. *Epilepsy Behav Rep* 2024;25:100636.
29. Shao B, Zheng B, Liu DD, et al. Seizure freedom after laser amygdalohippocampotomy guided by bilateral responsive neurostimulation in pediatric epilepsy: illustrative case. *J Neurosurg Case Lessons* 2022;4:Case22235.
30. Friedrichs-Maeder C, Proix T, Tcheng TK, Skarpaas T, Rao VR, Baud MO. Seizure cycles under pharmacotherapy. *Ann Neurol* 2024;95:743–753.
31. Privitera MD, Mendoza LC, Carrazana E, Rabinowicz AL. Intracerebral electrographic activity following a single dose of diazepam nasal spray: a pilot study. *Epilepsia Open* 2024;9:380–387.
32. Skelton HM, Brandman DM, Bullinger K, Isbaine F, Gross RE. Distinct biomarkers of ANT stimulation and seizure freedom in an epilepsy patient with ambulatory hippocampal electrocorticography. *Stereotact Funct Neurosurg* 2023;101:349–358.
33. Khambhati AN, Chang EF, Baud MO, Rao VR. Hippocampal network activity forecasts epileptic seizures. *Nat Med* 2024;30:2787–2790.
34. Proix T, Truccolo W, Leguía MG, et al. Forecasting seizure risk in adults with focal epilepsy: a development and validation study. *Lancet Neurol* 2021;20:127–135.
35. Baud MO, Kleen JK, Mirro EA, et al. Multi-day rhythms modulate seizure risk in epilepsy. *Nat Commun* 2018;9:88.
36. Gregg NM, Pal Attia T, Nasser M, et al. Seizure occurrence is linked to multiday cycles in diverse physiological signals. *Epilepsia* 2023;64:1627–1639.
37. Ilyas A, Hoffman C, Vakilna Y, et al. Forecasting seizure clusters from chronic ambulatory electrocorticography. *Epilepsia* 2022;63:e106–e111.
38. Wang ET, Chiang S, Cleboski S, Rao VR, Vannucci M, Haneef Z. Seizure count forecasting to aid diagnostic testing in epilepsy. *Epilepsia* 2022;63:3156–3167.
39. Oster JM, Tatum P, Monigan C, Kryzanski J. Seizures noted by responsive neurostimulation from e-cigarette use (vaping). *J Clin Neurophysiol* 2022;39:1–3.
40. Blond BN, Schindler EAD. Case report: psychedelic-induced seizures captured by intracranial electrocorticography. *Front Neurol* 2023;14:1214969.
41. Kundu B, Charlebois CM, Anderson DN, Peters A, Rolston JD. Chronic intracranial recordings after resection for epilepsy reveal a “running down” of epileptiform activity. *Epilepsia* 2023;64:e135–e142.
42. Quraishi IH, Brown FC, Johnson MH, Hirsch LJ. Hippocampal recording via the RNS system reveals marked ipsilateral activation of epileptiform activity during Wada testing. *Epilepsy Behav* 2022;134:108854.
43. Ernst LD, Steffan PJ, Srikanth P, et al. Electroencephalography analysis in patients with dual neurostimulators supports desynchronization as a mechanism of action for acute vagal nerve stimulator stimulation. *J Clin Neurophysiol* 2023;40:37–44.
44. Sellers KK, Khambhati AN, Stapper N, et al. Closed-loop neurostimulation for biomarker-driven, personalized treatment of major depressive disorder. *J Vis Exp*. 2023 Jul 7;197. doi:10.3791/65177.
45. Stangl M, Maoz SL, Suthana N. Mobile cognition: imaging the human brain in the ‘real world’. *Nat Rev Neurosci* 2023;24:347–362.
46. Kellogg MA, Ernst LD, Spencer DC, et al. Dual treatment of refractory focal epilepsy and obsessive-compulsive disorder with intracranial responsive neurostimulation. *Neurol Clin Pract* 2024;14:e200318.
47. Wu H, Adler S, Azagury DE, et al. Brain-responsive neurostimulation for loss of control eating: early feasibility study. *Neurosurgery* 2020;87:1277–1288.
48. Shivacharan RS, Rolle CE, Barbosa DAN, et al. Pilot study of responsive nucleus accumbens deep brain stimulation for loss-of-control eating. *Nat Med* 2022;28:1791–1796.
49. Scangos KW, Khambhati AN, Daly PM, et al. Closed-loop neuro-modulation in an individual with treatment-resistant depression. *Nat Med* 2021;27:1696–1700.
50. Gill JL, Schneiders JA, Stangl M, et al. A pilot study of closed-loop neuromodulation for treatment-resistant post-traumatic stress disorder. *Nat Commun* 2023;14:2997.
51. Ojemann WKS, Scheid BH, Mouchtaris S, et al. Resting-state background features demonstrate multidien cycles in long-term EEG device recordings. *Brain Stimul* 2023;16:1709–1718.
52. Chiang S, Khambhati AN, Tcheng TK, et al. State-dependent effects of responsive neurostimulation depend on seizure localization. *Brain* 2025;148:521–532.
53. Chiang S, Khambhati AN, Wang ET, Vannucci M, Chang EF, Rao VR. Evidence of state-dependence in the effectiveness of responsive neurostimulation for seizure modulation. *Brain Stimul* 2021;14:366–375.
54. Frauscher B, Bartolomei F, Baud MO, Smith RJ, Worrell G, Lundstrom BN. Stimulation to probe, excite, and inhibit the epileptic brain. *Epilepsia* 2023;64:S49–S61.
55. Khambhati AN, Shafi A, Rao VR, Chang EF. Long-term brain network reorganization predicts responsive neurostimulation outcomes for focal epilepsy. *Sci Transl Med* 2021;13:eabf6588.
56. Fan JM, Lee AT, Kudo K, et al. Network connectivity predicts effectiveness of responsive neurostimulation in focal epilepsy. *Brain Commun* 2022;4:fcac104.

57. Joshi RB, Zaveri HP. Prognostication of responsive neurostimulation system responsiveness using presurgical magnetoencephalography. *Brain Commun* 2022;4:fcac114.
58. Aiello G, Ledergerber D, Dubcek T, et al. Functional network dynamics between the anterior thalamus and the cortex in deep brain stimulation for epilepsy. *Brain* 2023;146:4717–4735.
59. Lundstrom BN, Van Gompel J, Britton J, et al. Chronic subthreshold cortical stimulation to treat focal epilepsy. *JAMA Neurol* 2016;73:1370–1372.
60. Lundstrom BN, Gompel JV, Khadjevand F, Worrell G, Stead M. Chronic subthreshold cortical stimulation and stimulation-related EEG biomarkers for focal epilepsy. *Brain Commun* 2019;1:fcz010.
61. Harrison DJ, Oushy S, Gregg NM, Lundstrom BN, Van Gompel JJ. Stereotactic depth electrode placement for chronic subthreshold cortical stimulation: surgical technique video. *Neurosurg Focus Video* 2024;11:V10.
62. Owens MR, Sather M, Fisher TL. Clinical outcomes following responsive neurostimulation implantation: a single center experience. *Front Neurol* 2023;14:1240380.
63. Ikegaya N, Aung T, Mallela A, Hect JL, Damiani A, Gonzalez-Martinez JA. Thalamic stereoelectroencephalography for neuromodulation target selection: proof of concept and review of literature of pulvinar direct electrical stimulation. *Epilepsia* 2024;65:e79–e86.
64. Gadot R, Korst G, Shofty B, Gavvala JR, Sheth SA. Thalamic stereoelectroencephalography in epilepsy surgery: a scoping literature review. *J Neurosurg* 2022;137:1210–1225.
65. Wu TQ, Kaboodvand N, McGinn RJ, et al. Multisite thalamic recordings to characterize seizure propagation in the human brain. *Brain* 2023;146:2792–2802.
66. McGinn R, Von Stein EL, Datta A, et al. Ictal involvement of the pulvinar and the anterior nucleus of the thalamus in patients with refractory epilepsy. *Neurology* 2024;103:e210039.
67. Edmonds B, Miyakoshi M, Gianmaria Remore L, et al. Characteristics of ictal thalamic EEG in pediatric-onset neocortical focal epilepsy. *Clin Neurophysiol* 2023;154:116–125.
68. Bernabei JM, Litt B, Cajigas I. Thalamic stereo-EEG in epilepsy surgery: where do we stand?. *Brain* 2023;146:2663–2665.
69. Gregg NM, Valencia GO, Huang H, et al. Thalamic stimulation induced changes in effective connectivity. *medRxiv*. 2024. doi:10.1101/2024.03.03.24303480.
70. Geller EB, Skarpaas TL, Gross RE, et al. Brain-responsive neurostimulation in patients with medically intractable mesial temporal lobe epilepsy. *Epilepsia* 2017;58:994–1004.
71. Charlebois CM, Anderson DN, Johnson KA, et al. Patient-specific structural connectivity informs outcomes of responsive neurostimulation for temporal lobe epilepsy. *Epilepsia* 2022;63:2037–2055.
72. Bondallaz P, Boëx C, Rossetti AO, et al. Electrode location and clinical outcome in hippocampal electrical stimulation for mesial temporal lobe epilepsy. *Seizure* 2013;22:390–395.
73. Eichert N, DeKraker J, Howard AFD, et al. Hippocampal connectivity patterns echo macroscale cortical evolution in the primate brain. *Nat Commun* 2024;15:5963.
74. Spencer SS. Neural networks in human epilepsy: evidence of and implications for treatment. *Epilepsia* 2002;43:219–227.
75. Piper RJ, Richardson RM, Worrell G, et al. Towards network-guided neuromodulation for epilepsy. *Brain* 2022;145:3347–3362.
76. Khambhati AN, Kahn AE, Costantini J, et al. Functional control of electrophysiological network architecture using direct neurostimulation in humans. *Netw Neurosci* 2019;3:848–877.
77. Scheid BH, Ashourvan A, Stiso J, et al. Time-evolving controllability of effective connectivity networks during seizure progression. *Proc Natl Acad Sci U S A* 2021;118:e2006436118.
78. Lüders HO, Najm I, Nair D, Widdess-Walsh P, Bingman W. The epileptogenic zone: general principles. *Epileptic Disord* 2006;8:S1–S9.
79. Schulze-Bonhage A, Nitsche MA, Rotter S, Focke NK, Rao VR. Neurostimulation targeting the epileptic focus: current understanding and perspectives for treatment. *Seizure* 2024;117:183–192.
80. Skelton HM, Bullinger K, Isbaine F, Lau JC, Willie JT, Gross RE. Optimal hippocampal targeting in responsive neurostimulation for mesial temporal lobe epilepsy. *J Neurosurg* 2024;141:1105–1114.
81. Warren AEL, Dalic LJ, Bulluss KJ, BappSci AR, Thevathasan W, Archer JS. The optimal target and connectivity for deep brain stimulation in lennox-gastaut syndrome. *Ann Neurol* 2022;92:61–74.
82. Kobayashi K, Taylor KN, Shahabi H, et al. Effective connectivity relates seizure outcome to electrode placement in responsive neurostimulation. *Brain Commun* 2024;6:fcac035.
83. Weiss SA, Sperling MR, Engel J, et al. Simulated resections and responsive neurostimulator placement can optimize postoperative seizure outcomes when guided by fast ripple networks. *Brain Commun* 2024;6:fcac367.
84. Nunna RS, Borghesi A, Brahima BC, et al. Responsive neurostimulation of the mesial temporal white matter in bilateral temporal lobe epilepsy. *Neurosurgery* 2021;88:261–267.
85. Zheng Y, Jiang Z, Ping A, et al. Acute seizure control efficacy of multi-site closed-loop stimulation in a temporal lobe seizure model. *IEEE Trans Neural Syst Rehabil Eng* 2019;27:419–428.
86. Yang AI, Isbaine F, Alwaki A, Gross RE. Multitarget deep brain stimulation for epilepsy. *J Neurosurg* 2024;140:210–217.
87. Warren AEL, Butson CR, Hook MP, et al. Targeting thalamocortical circuits for closed-loop stimulation in Lennox-Gastaut syndrome. *Brain Commun* 2024;6:fcac161.
88. Huang Y, Zelmann R, Hadar P, et al. Theta-burst direct electrical stimulation remodels human brain networks. *Nat Commun* 2024;15:6982.
89. Zheng B, Liu DD, Theyel BB, et al. Thalamic neuromodulation in epilepsy: a primer for emerging circuit-based therapies. *Expert Rev Neurother* 2023;23:123–140.
90. Manjunatha RT, Vakilina YS, Chaitanya G, Alamoudi O, Ilyas A, Pati S. Advancing the frontiers of thalamic neuromodulation: a review of emerging targets and paradigms. *Epilepsy Res* 2023;196:107219.
91. Salanova V, Sperling MR, Gross RE, et al. The SANTÉ study at 10 years of follow-up: effectiveness, safety, and sudden unexpected death in epilepsy. *Epilepsia* 2021;62:1306–1317.
92. Nanda P, Sisterson N, Walton A, et al. Centromedian region thalamic responsive neurostimulation mitigates idiopathic generalized and multifocal epilepsy with focal to bilateral tonic-clonic seizures. *Epilepsia* 2024;65:2626–2640.
93. Nathan CL, Gavvala JR, Chaitanya G, et al. High-frequency stimulation of the centromedian thalamic nucleus aborts seizures and ictal apnea. *J Clin Neurophysiol* 2024;41:570–574.
94. Fields MC, Eka O, Schreckinger C, et al. A multicenter retrospective study of patients treated in the thalamus with responsive neurostimulation. *Front Neurol* 2023;14:1202631.
95. Gummadavelli A, Zaveri HP, Spencer DD, Gerrard JL. Expanding brain-computer interfaces for controlling epilepsy networks: novel thalamic responsive neurostimulation in refractory epilepsy. *Front Neurosci* 2018;12:474.
96. Park S, Permezel F, Agashe S, et al. Centromedian thalamic deep brain stimulation for idiopathic generalized epilepsy: connectivity and target optimization. *Epilepsia* 2024;65:e197–e203.
97. Remore LG, Rifi Z, Nariai H, et al. Structural connections of the centromedian nucleus of thalamus and their relevance for neuro-modulation in generalized drug-resistant epilepsy: insight from a tractography study. *Ther Adv Neurol Disord* 2023;16:17562864231202064.
98. Zillgitt AJ, Haykal MA, Chehab A, Staudt MD. Centromedian thalamic neuromodulation for the treatment of idiopathic generalized epilepsy. *Front Hum Neurosci* 2022;16:907716.
99. Burdette D, Mirro EA, Lawrence M, Patra SE. Brain-responsive corticothalamic stimulation in the pulvinar nucleus for the treatment of regional neocortical epilepsy: a case series. *Epilepsia Open* 2021;6:611–617.
100. Burdette D, Patra S, Johnson L. Corticothalamic responsive neurostimulation for focal epilepsy: a single-center experience. *J Clin Neurophysiol* 2024;41:630–639.
101. Feigen CM, Eskandar EN. Responsive thalamic neurostimulation: a systematic review of a promising approach for refractory epilepsy. *Front Hum Neurosci* 2022;16:910345.
102. Abdulrazeq H, Kimata AR, Blum A, Malik AN, Asaad WF. Exploring the role of the pulvinar nucleus of the thalamus in occipital lobe epilepsy: a case report. *Cureus* 2024;16:e52534.
103. Wong GM, Hofmann K, Shlobin NA, Tsuchida TN, Gaillard WD, Oluigbo CO. Stimulation of the pulvinar nucleus of the thalamus in epilepsy: a systematic review and individual patient data (IPD) analysis. *Clin Neurol Neurosurg* 2023;235:108041.
104. Beaudreault CP, Muh CR, Naftchi A, et al. Responsive neurostimulation targeting the anterior, centromedian and pulvinar thalamic nuclei

- and the detection of electrographic seizures in pediatric and young adult patients. *Front Hum Neurosci* 2022;16:876204.
105. Gonzalez-Martinez J, Damiani A, Nouduri S, et al. Thalamocortical hodology to personalize electrical stimulation for focal epilepsy. *Res Sq*. 2024 Nov 28. doi:10.21203/rs.3.rs-5507011/v1.
 106. Bradley C, Nydam AS, Dux PE, Mattingley JB. State-dependent effects of neural stimulation on brain function and cognition. *Nat Rev Neurosci* 2022;23:459–475.
 107. Cagnan H, Pedrosa D, Little S, et al. Stimulating at the right time: phase-specific deep brain stimulation. *Brain* 2017;140:132–145.
 108. Scangos KW, Makhoul GS, Sugrue LP, Chang EF, Krystal AD. State-dependent responses to intracranial brain stimulation in a patient with depression. *Nat Med* 2021;27:229–231.
 109. Ezzyat Y, Kragel JE, Burke JF, et al. Direct brain stimulation modulates encoding states and memory performance in humans. *Curr Biol* 2017;27:1251–1258.
 110. Bergmann TO. Brain state-dependent brain stimulation. *Front Psychol* 2018;9:2108.
 111. Fan Y, Wei X, Lu M, Wang J, Yi G. State-dependent modulation of low-threshold-current-regulated dendritic Ca(2+) response in thalamic reticular neurons with extracellular electric fields. *Sci Rep* 2023;13:16485.
 112. Suresh S, Chaitanya G, Kachhvhah AD, Vashin V, Saranathan M, Pati S. Case report: nocturnal low-frequency stimulation of the centromedian thalamic nucleus improves sleep quality and seizure control. *Front Hum Neurosci* 2024;18:1392100.
 113. Voges BR, Schmitt FC, Hamel W, et al. Deep brain stimulation of anterior nucleus thalami disrupts sleep in epilepsy patients. *Epilepsia* 2015;56:e99–e103.
 114. Chiang S, Moss R, Black AP, et al. Evaluation and recommendations for effective data visualization for seizure forecasting algorithms. *JAMA Open* 2021;4:ooab009.
 115. Anderson DN, Charlebois CM, Smith EH, et al. Closed-loop stimulation in periods with less epileptiform activity drives improved epilepsy outcomes. *Brain* 2024;147:521–531.
 116. Leguia MG, Rao VR, Kleen JK, Baud MO. Measuring synchrony in bio-medical timeseries. *Chaos* 2021;31:013138.
 117. Leguia MG, Andrzejak RG, Rummel C, et al. Seizure cycles in focal epilepsy. *JAMA Neurol* 2021;78:454–463.
 118. Karoly PJ, Goldenholz DM, Freestone DR, et al. Circadian and circaseptan rhythms in human epilepsy: a retrospective cohort study. *Lancet Neurol* 2018;17:977–985.
 119. Rao VR, G Leguia M, Tcheng TK, Baud MO. Cues for seizure timing. *Epilepsia* 2021;62:S15–S31.
 120. Karoly PJ, Ung H, Grayden DB, et al. The circadian profile of epilepsy improves seizure forecasting. *Brain* 2017;140:2169–2182.
 121. Karoly PJ, Freestone DR, Boston R, et al. Interictal spikes and epileptic seizures: their relationship and underlying rhythmicity. *Brain* 2016;139:1066–1078.
 122. Karoly PJ, Rao VR, Gregg NM, et al. Cycles in epilepsy. *Nat Rev Neurol* 2021;17:267–284.
 123. Baud MO, Proix T, Gregg NM, et al. Seizure forecasting: bifurcations in the long and winding road. *Epilepsia* 2023;64:S78–S98.
 124. Donoghue T, Haller M, Peterson EJ, et al. Parameterizing neural power spectra into periodic and aperiodic components. *Nat Neurosci* 2020;23:1655–1665.
 125. Charlebois CM, Anderson DN, Smith EH, et al. Circadian changes in aperiodic activity are correlated with seizure reduction in patients with mesial temporal lobe epilepsy treated with responsive neurostimulation. *Epilepsia* 2024;65:1360–1373.
 126. Gregg NM, Sladky V, Nejedly P, et al. Thalamic deep brain stimulation modulates cycles of seizure risk in epilepsy. *Sci Rep* 2021;11:24250.
 127. Arcot Desai S, Tcheng TK, Morrell MJ. Quantitative electrocorticographic biomarkers of clinical outcomes in mesial temporal lobe epileptic patients treated with the RNS® system. *Clin Neurophysiol* 2019;130:1364–1374.
 128. Merk T, Köhler R, Peterson V, et al. Invasive neurophysiology and whole brain connectomics for neural decoding in patients with brain implants. *Res Sq*. 2022 Mar 4;12. doi:10.3389/fneur.2021.703797.
 129. Manzouri F, Zöllin M, Schillinger S, et al. A comparison of energy-efficient seizure detectors for implantable neurostimulation devices. *Front Neurol* 2021;12:703797.
 130. Oehm CR, Cernera S, Hammer LH, et al. Chronic adaptive deep brain stimulation versus conventional stimulation in Parkinson's disease: a blinded randomized feasibility trial. *Nat Med* 2024;30:3345–3356.
 131. Zhu B, Shin U, Shoaran M. Closed-loop neural prostheses with on-chip intelligence: a review and a low-latency machine learning model for brain state detection. *IEEE Trans Biomed Circuits Syst* 2021;15:877–897.
 132. Herbozo Contreras LF, Truong ND, Eshraghian JK, et al. Neuromorphic neuromodulation: towards the next generation of closed-loop neurostimulation. *PNAS Nexus* 2024;3:pgae488.
 133. Zhao Z, Cea C, Gelinas JN, Khodagholy D. Responsive manipulation of neural circuit pathology by fully implantable, front-end multiplexed embedded neuroelectronics. *Proc Natl Acad Sci USA* 2021;118:e2022659118.
 134. Chandrabhatla AS, Pomeranec JJ, Horgan TM, Wat EK, Ksendzovsky A. Landscape and future directions of machine learning applications in closed-loop brain stimulation. *NPJ Digit Med* 2023;6:79.
 135. Rønberg SN, Esteller R, Tcheng TK, et al. Acute effects of brain-responsive neurostimulation in drug-resistant partial onset epilepsy. *Clin Neurophysiol* 2021;132:1209–1220.
 136. Sohal VS, Sun FT. Responsive neurostimulation suppresses synchronized cortical rhythms in patients with epilepsy. *Neurosurg Clin North America* 2011;22:481–488.
 137. Alcalá-Zermeno JL, Starnes K, Gregg NM, Worrell G, Lundstrom BN. Responsive neurostimulation with low-frequency stimulation. *Epilepsia* 2023;64:e16–e22.
 138. Kokkinos V, Sisterson ND, Wozny TA, Richardson RM. Association of closed-loop brain stimulation neurophysiological features with seizure control among patients with focal epilepsy. *JAMA Neurol* 2019;76:800–808.
 139. Kleen JK, Rao VR. Chapter 12 - managing neurostimulation for epilepsy. In: Marks WJ, Ostrem JL, eds. *Deep brain stimulation management*. United Kingdom: Cambridge University Press & Assessment; 2022:177–197.
 140. Arcot Desai S, Afzal MF, Barry W, et al. Expert and deep learning model identification of iEEG seizures and seizure onset times. *Front Neurosci* 2023;17:1156838.
 141. Peterson V, Kokkinos V, Ferrante E, et al. Deep net detection and onset prediction of electrographic seizure patterns in responsive neurostimulation. *Epilepsia* 2023;64:2056–2069.
 142. Constantino AC, Sisterson ND, Zaher N, Urban A, Richardson RM, Kokkinos V. Expert-level intracranial electroencephalogram ictal pattern detection by a deep learning neural network. *Front Neurol* 2021;12:603868.
 143. Arcot Desai S, Tcheng T, Morrell M. Non-linear embedding methods for identifying similar brain activity in 1 million iEEG records captured from 256 RNS system patients. *Front Big Data* 2022;5:840508.
 144. Lhatoo SD, Bernasconi N, Blumcke I, et al. Big data in epilepsy: clinical and research considerations. Report from the epilepsy big data task force of the international league against epilepsy. *Epilepsia* 2020;61:1869–1883.
 145. Basu I, Robertson MM, Crocker B, et al. Consistent linear and non-linear responses to invasive electrical brain stimulation across individuals and primate species with implanted electrodes. *Brain Stimul* 2019;12:877–892.
 146. Groppa S, Gonzalez-Escamilla G, Tinkhauser G, et al. Perspectives of implementation of closed-loop deep brain stimulation: from neurological to psychiatric disorders. *Stereotact Funct Neurosurg* 2024;102:40–54.
 147. Sellers KK, Cohen JL, Khambhati AN, et al. Closed-loop neurostimulation for the treatment of psychiatric disorders. *Neuropsychopharmacology* 2024;49:163–178.
 148. Kossoff EH, Ritzl EK, Politsky JM, et al. Effect of an external responsive neurostimulator on seizures and electrographic discharges during subdural electrode monitoring. *Epilepsia* 2004;45:1560–1567.