Stimulating Solutions for Intractable Epilepsy

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Abstract
Implantable devices for controlling medically intractable seizures nondestructively are rapidly advancing. These offer reversible, potentially, restorative options beyond traditional, surgical procedures, which rely, largely on resection or ablation of selected brain sites. Several lines of investigation aimed at improving efficacy of these devices are discussed, ranging from identifying novel subcortical, white matter, or cell-type specific targets to engineering advances for adaptive techniques based on continuous, dynamic system analysis.

Keywords
electrical stimulation, intractable epilepsy, therapeutic devices, next-generation devices, epileptic networks

Treatments for pharmacoresistant epilepsy syndromes have largely focused on nonreversible surgical intervention, such as focal brain resection, ablation, or structural disconnection. The goal of reducing morbidity and creating nondestructive, reversible therapies has led to a series of implantable devices that deliver physiologically inspired electrical signals directly to the brain.¹ These have a history extending across decades, including stimulators targeting the cerebellum, left vagus nerve, and trigeminal nerve. These provide a much needed therapeutic alternative especially for patients facing a high risk of adverse cognitive effects from destructive therapy. The recent approvals of two new implantable devices, which have already become mainstays of epilepsy treatment, have helped to spur new progress in the field. These are the responsive neural stimulator (RNS; Neuropace Inc), which targets selected cortical or subcortical sites with tailored permanent electrode implants, and the Medtronic deep brain stimulation (DBS) device targeting the anterior nucleus of the thalamus (Medtronic Inc). As yet, however, the modest seizure-free rates achieved by these devices cannot match the benefits of traditional brain resection. Additionally, therapy optimization is a time-consuming process that may extend into periods of years, thus delaying clinical benefit. However, there is hope that these gaps may eventually close.

In a series of lectures presented at the Merritt-Putnam Symposium in the 2020 American Epilepsy Society Annual Meeting, three general investigative approaches to device efficacy were described: addressing network interactions inherent in focal epilepsies, identifying novel stimulation paradigms and targets, and expansion of device capabilities to permit dynamic adaptation in response to patient needs.
A Network Approach to Stimulation for Treating Focal Seizures

One approach is to devise a rational, systematic process for determining electrical stimulation parameters. Current strategies for generating DBS protocols utilized in both clinical and research applications have been largely empirical, in which a particular starting point for stimulation protocols is established ad hoc and then tweaked to improve efficacy. The parameter space for stimulation can be quite large: stimulation amplitude, duration, frequency, locations, and so on, can all be varied and used in unique combinations. Given this, such improvised modifications can be inefficient. In addition to complications associated with neuronal diversity and differing responses to stimulation parameters, we believe that there are at least two specific root causes for this state of affairs. First, stimulation protocols generally do not reflect the real-time dynamics of the brain's electrical state. Although some attempts at modulating the time of stimulation are being employed to improve the responsiveness of stimulation, the stimulation paradigm itself is still largely predetermined. Second, there is increasing evidence that the neural network circuitry that contributes to epileptic seizures in many cases may extend well beyond the designated focal region into other parts of the brain.

Dynamical analysis of endogenous neural coherence at multiple sites in the epileptic rat brain has been used to develop subject-specific DBS protocols that may lead to improved seizure control. A personalized form of DBS using dynamical biomarkers was used successfully to terminate seizures in a chronic rat model of temporal lobe epilepsy (TLE). Periods of significant change in multisite coherence occurred coincident with the time of seizure onset, and a different but related dynamic was observed in depth recordings from patients with TLE. Similar types of dynamics were also observed in depth recordings from patients with TLE. These dynamics could significantly vary between rodent subjects but be stable in time over many months. When DBS was applied at the locations and frequencies where high synchronization occurred at the time of natural seizure termination for that specific animal, exogenous stimulation could abruptly terminate a seizure significantly faster than stimulation that was not tailored to the subject. These and other results provide a pathway of personalizing DBS application tailored for the specific ictal pathology of each patient.

Techniques for Basic Science Studies of Targeted Seizure Intervention

Interventions that are highly specific for site and cell type may increase stimulation efficacy while reducing unwanted side effects. Such studies currently require highly specific experimental techniques such as closed-loop, on-demand optogenetics. Studies utilizing on-demand optogenetics have shown that a highly specific intervention, for example, targeting only dentate gyrus granule cells near the seizure focus, can be highly effective for controlling seizures. On-demand optogenetics can also be applied to areas remote from the site of injury or seizure focus, including the cerebellum. Experiments have revealed that excitation, but not inhibition, of the cerebellar fastigial nucleus is able to provide powerful inhibition of temporal lobe seizures, illustrating a benefit of optogenetic-based approaches, and the relatively straightforward control over the direction of modulation they provide. Moreover, selective excitation of only excitatory neurons in the fastigial nucleus provides greater seizure control than an approach that lacks cell-type specificity and broadly excites electrical stimulation of callosal fibers that are connected with that seizure focus was effective in reducing seizures. When compared with other neuromodulatory modalities including high-frequency stimulation of the focus or the anterior thalamic nucleus, callosal stimulation was significantly more efficacious in reducing seizures.

The above preclinical findings of fiber tract stimulation were translated into a proof-of-principle human trial. In that short-term trial, which was conducted during invasive monitoring in the epilepsy monitoring unit, LFS (5 Hz) of the human dorsal hippocampal commissure reduced temporal lobe seizures by 90%. As this fiber tract is very close to the posterior arching fornices, the target was termed the fornico-dorso-commissural (FDC) tract. Subsequently, a year-long single-blinded study with implantable pulse generators was done in four individuals with bilateral TLE using chronic 5 Hz electrical stimulation of the FDC. Two subjects became seizure-free, and repeated neuropsychological testing revealed preserved memory.

Although the FDC appears to be a good stimulation target in TLE, the piriform cortex may be an attractive target for neuromodulation regardless of the location of the seizure focus. The piriform cortex is a key structure for epileptogenicity related to chemical, electrical stimulation, kindling, and status epilepticus models in rodents and primates. It has a role in focal and generalized epilepsy networks and bears some similarities to the hippocampus histologically. In the kainic acid model, a model of severe intractable seizures, LFS of the piriform cortex resulted in almost complete cessation of seizures. In another study, the amplitudes of the evoked responses recorded in the contralateral hippocampus upon stimulation of the piriform cortex appeared to increase after acquisition of epileptogenicity. This amplification may suggest facilitation of interhemispheric seizure propagation pathways which utilize the piriform cortex as a key hub.

Novel Stimulation Approaches

Low-frequency stimulation (LFS) has been underutilized in epilepsy research but has shown recent promising results. In animal models of limbic and neocortical seizures, LFS of a white matter tract connected with a seizure focus can reduce seizures. In a rat model of TLE, LFS of the dorsal hippocampal commissure at 1 Hz reduced seizures by 90% during the two weeks of stimulation. Seizures continued to be reduced (57%) for two weeks after stimulation suggesting a significant carryover effect. In neocortical epilepsy induced by acute application of 4-aminopyridine in the rat somatosensory cortex, 20 Hz
fastigial neurons.\textsuperscript{25} This highlights an important concept: specificity of intervention may not only be important for reducing side effects, it may also be a means to directly improve the efficacy of interventions.

Although the excellent specificity of on-demand optogenetics has several benefits over traditional approaches, it is not currently a clinical option for the epilepsies.\textsuperscript{19,20,26} Electrical stimulation, however, is. Electrical stimulation of the cerebellum has been previously examined, in both human clinical trials and in a large number of animal studies (reviewed in the study by Streng and Krook-Magnuson,\textsuperscript{22} Fountas et al,\textsuperscript{27} and Miller\textsuperscript{28}). However, these studies were all done “open loop,”

![Figure 1](image-url)

\textbf{Figure 1.} Brain co-processor for integrating implanted sensing and stimulation devices with off-the-body computing resources. The system enables continuous tracking of physiological data coupled with adaptive electrical stimulation. Top) Schematic for bidirectional data transmission between implanted brain sensing and stimulation device integrated with local handheld computer (Epilepsy Patient Assist Device) and cloud environment. The integrated system provides a platform for real-time, continuous, remote ambulatory monitoring physiological data such as brain behavioral state (wake, sleep, and seizures), biomarker (eg, interictal discharges) and behavior (patient inputs, actigraphy, mood, memory), as well as device data (eg, battery status and telemetry). Bottom left) The electrophysiology data are wirelessly telemetered off the implant and processed. Bottom right) Web-based Epilepsy Dashboard enables review of immediate and long-term data trends from the device (eg, battery, electrode impedances), electrophysiology data, and patient inputs. The physician can quickly review and either confirm or reject automatically detected and patient-reported events.
where stimulation was not specifically timed to the seizure event. Additionally, stimulation parameters varied widely, often even within a single study. Therefore, it may be that robust, consistent, seizure inhibition may be possible, if the correct combination of stimulation parameters can be identified. Methods of tailoring closed-loop approaches, such as Bayesian Optimization, may be means to determine which sets of electrical stimulation parameters can be effective, either for an individual or, potentially, for any given stimulation site. Optimization approaches may also help in the making the next generation of implantable systems more individualized and responsive to patients’ needs.

**Next-Generation Implantable Systems**

To improve the translation of current implantable system technology, several fundamental issues should be resolved. Most existing therapies do not take full advantage of the capability of bioelectronics to dynamically adjust stimulation parameters in response to the patient’s needs. Many predicate algorithms rely on concepts from cardiac pacemakers, even while the underlying physiology is very different. The lack of device responsivity is compounded by the absence of objective, reliable outcome measures. The absence of an immediate physiometer, unlike the case with movement disorders, can make therapy optimization a long and tortuous process. Although the effectiveness of DBS and RNS for epilepsy is established, it is still an intervention that requires invasive surgery, and fear of complications frightens many patients; clearly, there is a desire to lower the invasiveness of therapeutic systems. Finally, like pharmaceuticals, the economic incentives of personalized medicine that bioelectronics might enable still needs alignment across health care stakeholders.

Including collaborative platforms as part of next-generation systems is a promising route to addressing the challenges and opportunities of bioelectronic medicines, when bridging basic science, advanced technology, and health care economics. Bioelectronic platforms can create a self-reinforcing innovation framework—from designing bespoke, instrumented implantable platforms that enable novel clinical neuroscience, to applying these platforms and the resulting science to prototype new therapies—that can help catalyze new treatments for disease. For example, recent device advances include continuous streaming of brain sensing data that opens a new vista of adaptive therapy applications, including the application of a distributed brain co-processor providing an intuitive, bidirectional interface between the implanted device, patient, and physician in both canine and human drug-resistant epilepsy. Automated classifiers running on a handheld tablet computer and distributed cloud computing resource provide near-real-time assessment of behavioral state (awake and sleep), interictal epileptiform discharges, and seizures to guide adaptive electrical stimulation. Devices that include recognition of circadian and multiden rhythms are also being explored in research settings, temporally aware devices provide a mechanism to apply chronotherapy in disease states such as epilepsy where rhythm-specific signatures are being identified with new sensing-enabled devices.

Platform tools like this (Figure 1) are currently enabling new discovery models, aligned with the vision of global activities such as the NIH BRAIN initiative. The breadth of studies reflects the diversity of challenges created by neurological disorders, but also the hope that bioelectronic platforms can help address them.

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**References**

1. Famm K, Litt B, Tracey KJ, Boydgen ES, Slouai M. A jump-start for electroceuticals. Nature. 2013;496(7444):159-161.
2. Bertram EH. Temporal lobe epilepsy: where do the seizures really begin? Epilepsy Behav. 2009;14(suppl 1):32-37.
3. Sobayo T, Mogul DJ. Should stimulation parameters be individualized to stop seizures: evidence in support of this approach. Epilepsia. 2016;57(1):131-140.
4. Fine AS, Nicholls DP, Mogul DJ. Assessing instantaneous synchrony of nonlinear nonstationary oscillators in the brain. J Neurosci Methods. 2010;186(1):42-51.
5. Sobayo T, Fine AS, Gunmar E, Kazlauskas C, Nicholls D, Mogul DJ. Synchrony dynamics across brain structures in limbic epilepsy vary between initiation and termination phases of seizures. IEEE Trans Biomed Eng. 2013;60(3):821-829.
6. Farahmand S, Sobayo T, Mogul DJ. Noise-assisted multivariate EMD-based mean-phase coherence analysis to evaluate phase-synchrony dynamics in epilepsy patients. IEEE Trans Neural Syst Rehabil Eng. 2018;26(12):2270-2279.
7. Arrais M, Modolo J, Mogul D, Wendling F. Design of optimal multi-site brain stimulation protocols via neuro-inspired epilepsy models for abatement of interictal discharges. J Neural Eng. 2020. doi:10.1088/1741-2552/abd049
8. Rashid S, Pho G, Czigler M, Wizer MA, Durand DM. Low frequency stimulation of ventral hippocampal commissures reduces seizures in a rat model of chronic temporal lobe epilepsy. Epilepsia. 2012;53(1):147-156.
9. Couturier NH, Durand DM. Comparison of fiber tract low frequency stimulation to focal and ANT stimulation in an acute rat model of focal cortical seizures. *Brain Stimul.* 2020;13(2):499-506.

10. Kounbeissi MZ, Kahriman E, Syed TU, Miller J, Durand DM. Low-frequency electrical stimulation of a fiber tract in temporal lobe epilepsy. *Ann Neurol.* 2013;74(2):223-231.

11. Koepf M, Galovic M. Functional imaging of the piriform cortex in focal epilepsy. *Exp Neurol.* 2020;330:113305.

12. de Curtis M, Uva L, Lèvesque M, Biella G, Avoli M. Piriform cortex ictogenicity in vitro. *Exp Neurol.* 2019;321:113014.

13. Cheng H, Wang Y, Chen J, Chen Z. The piriform cortex in epilepsy: what we learn from the kindling model. *Exp Neurol.* 2020;324:113137.

14. Young JC, Vaughan DN, Nasser HM, Jackson GD. Anatomical imaging of the piriform cortex in epilepsy. *Exp Neurol.* 2019;320:113013.

15. Bayat A, Skopin MD, Joshi S, et al. Effects of low-frequency electrical stimulation of the anterior piriform cortex on kainate-induced seizures in rats. *Epilepsy Behav.* 2017;72:1-7.

16. Skopin MD, Bayat A, Kurada L, et al. Epileptogenesis-induced changes of hippocampal-piriform connectivity. *Seizure.* 2020;81:1-7.

17. Krook-Magnuson E, Armstrong C, Bui A, Lew S, Oijala M, Soltész I. In vivo evaluation of the dentate gate theory in epilepsy. *J Physiol.* 2015;593(10):2379-2388.

18. Krook-Magnuson E, Armstrong C, Oijala M, Soltész I. On-demand optogenetic control of spontaneous seizures in temporal lobe epilepsy. *Nat Commun.* 2013;4:1376.

19. Christensen Wick Z, Krook-Magnuson E. Specificity, versatility, and continual development: the power of optogenetics for epilepsy research. *Front Cell Neurosci.* 2018;12:151.

20. Krook-Magnuson E, Soltész I. Beyond the hammer and the scalpel: selective circuit control for the epilepsies. *Nat Neurosci.* 2015;18(3):331-338.

21. Paz JT, Davidson TJ, Frechette ES, et al. Closed-loop optogenetic control of thalamus as a tool for interrupting seizures after cortical injury. *Nat Neurosci.* 2013;16(1):64-70.

22. Streng ML, Krook-Magnuson E. The cerebellum and epilepsy. *Epilepsy Behav.* 2020;106909. doi:10.1016/j.yebeh.2020.106909

23. Krook-Magnuson E, Szabo GG, Armstrong C, Oijala M, Soltész I. Cerebellar directed optogenetic intervention inhibits spontaneous hippocampal seizures in a mouse model of temporal lobe epilepsy. *eNeuro.* 2014;1(1).

24. Kros L, Eelkman Rooja OH, Spanke JK, et al. Cerebellar output controls generalized spike-and-wave discharge occurrence. *Ann Neurol.* 2015;77(6):1027-1049.

25. Streng ML, Krook-Magnuson E. Excitation, but not inhibition, of the fastigial nucleus provides powerful control over temporal lobe seizures. *J Physiol.* 2020;598(1):171-187.

26. Kullmann DM, Schorge S, Walker MC, Wykes RC. Gene therapy in epilepsy—is it time for clinical trials? *Nat Rev Neurol.* 2014;10(5):300-304.

27. Fountas KN, Kapsalaki E, Hadjigeorgiou G. Cerebellar stimulation in the management of medically intractable epilepsy: a systematic and critical review. *Neurosurg Focus.* 2010;29(2):E8.

28. Miller JW. The role of mesencephalic and thalamic arousal systems in experimental seizures. *Prog Neurobiol.* 1992;39(2):155-178.

29. Nagaraj V, Lee ST, Krook-Magnuson E, et al. Future of seizure prediction and intervention: closing the loop. *J Clin Neurophysiol.* 2015;32(3):194-206.

30. Schulze-Bonhage A. Long-term outcome in neurostimulation of epilepsy. *Epilepsy Behav.* 2019;91:25-29.

31. Kremen V, Brinkmann BH, Kim I, et al. Continuous active probing and modulation of neural networks with a wireless implantable system. In 2017 IEEE Biomedical Circuits and Systems Conference (BioCAS); Turin, Italy; October 19-21, 2017. IEEE. 1-4. doi:10.1109/BIOCAS.2017.8325195

32. Volkman J, Herzog J, Kopper F, Deuschl G. Introduction to the programming of deep brain stimulators. *Mov Disord.* 2002;17(suppl 3):S181-S187.

33. Kim MR, Yun JY, Jeon B, et al. Patients’ reluctance to undergo deep brain stimulation for Parkinson’s disease. *Parkinsonism Relat Disord.* 2016;23:91-94.

34. Thakor NV. Translating the brain-machine interface. *Sci Transl Med.* 2015;7(210):210ps17.

35. Davis JC, Furstenthal L, Desai AA, et al. The microeconomics of personalized medicine: today’s challenge and tomorrow’s promise. *Nat Rev Drug Discov.* 2009;8(4):279-286.

36. Benton DA, Dawes HE, Worrell GA, Starr PA, Denison TJ. Developing collaborative platforms to advance neurotechnology and its translation. *Neuron.* 2020;108(2):286-301.

37. Kremen V, Brinkmann BH, Kim I, et al. Integrating brain implants with local and distributed computing devices: a next generation epilepsy management system. *IEEE J Transl Eng Health Med.* 2018;6:2500112.

38. Gilron R, Little S, Perrone R, et al. Chronic wireless streaming of invasive neural recordings at home for circuit discovery and adaptive stimulation. *bioRxiv.* 2020. http://biorxiv.org/lookup/doi/10.1101/2020.02.13.948349. doi:10.1101/2020.02.13.948349

39. Sladky V, Nejedly P, Mivalt F, et al. Distributed brain co-processor for neurophysiologic tracking and adaptive stimulation: application to drug resistant epilepsy. *bioRxiv.* 2021. http://biorxiv.org/lookup/doi/10.1101/2021.03.08.434476. doi:10.1101/2021.03.08.434476

40. Toth R, Zamora M, Ottaway J, et al. DyNeuMo Mk-2: an investigational circadian locked neuromodulator with responsive stimulation for applied chronobiology. In: 2020 IEEE International Conference on Systems, Man, and Cybernetics (SMC); Toronto, Canada; October 11-14, 2020. IEEE:3433-3440. doi:10.1109/SMC42975.2020.9283187

41. Baud MO, Kleen JK, Mirro EA, et al. Multi-day rhythms modulate seizure risk in epilepsy. *Nat Commun.* 2018;9(1):88.

42. Gregg NM, Nasser M, Kremen V, et al. Circadian and multiday seizure periodicities, and seizure clusters in canine epilepsy. *Brain Commun.* 2020;2(1):fca008.

43. Jorgenson LA, Newsome WT, Anderson DJ, et al. The BRAIN initiative: developing technology to catalyse neuroscience discovery. *Philos Trans R Soc Lond B Biol Sci.* 2015;370(1668):20140164.