Epilepsy Currents
2024, Vol. 24(2) 135-137

DOI: 10.1177/15357597241233221
journals.sagepub.com/home/epi
Sage

Closing the Loop for Precise Seizure Control

Closed-Loop Direct Control of Seizure Focus in a Rodent Model of Temporal Lobe Epilepsy via Localized Electric Fields Applied Sequentially

Kang W, Ju C, Joo J, Lee J, Shon Y-M, Park S-M. *Nat Commun*. 2022;13(1):7805. doi:10.1038/s41467-022-35540-7

Direct electrical stimulation of the seizure focus can achieve the early termination of epileptic oscillations. However, direct intervention of the hippocampus, the most prevalent seizure focus in temporal lobe epilepsy is thought to be not practicable due to its large size and elongated shape. Here, in a rat model, we report a sequential narrow-field stimulation method for terminating seizures, while focusing stimulus energy at the spatially extensive hippocampal structure. The effects and regional specificity of this method were demonstrated via electrophysiological and biological responses. Our proposed modality demonstrates spatiotemporal preciseness and selectiveness for modulating the pathological target region which may have potential for further investigation as a therapeutic approach.

Commentary

Anti-seizure medications (ASM), special diets, and surgery represent traditional treatment options for epilepsy. In the past decade, neuromodulation or neurostimulation has gained increasing attention for its implication in epilepsy therapies.[1] Commonly used neurostimulation approaches include vagus nerve stimulation, deep brain stimulation (DBS), and responsive neurostimulation (RNS), among others. These approaches offer viable treatment options for drug-refractory epilepsy and present numerous advantages over ASM and surgery. Firstly, neurostimulation can intervene only when needed. The unpredictable nature of seizures poses a unique opportunity for developing an ideal treatment strategy that acts only on an "as-needed" basis. On-demand neurostimulation like closed-loop DBS and RNS, initiated following real-time seizure detection, can minimize disruptions to normal interictal activities and reduce the side effects commonly associated with ASM. Secondly, neurostimulation is reversible and adjustable. Instead of surgically removing, ablating, and disconnecting the seizure onset zone, neurostimulation halts seizures by manipulating neural circuits and networks with a greater degree of control. The manipulation can be terminated as needed. The stimulation site and parameters can also be tuned based on an individual's responses across the course of treatment. The closed-loop approach also mitigates stimulation tolerance inherent in open-loop (e.g., continuous) stimulation. As we embrace the rise of the "neurostimulation era", precise spatiotemporal control of stimulation is imperative for a better outcome with minimal "off-target" effects.

In this critical proof-of-concept study, Kang et al. present a new sequentially organized microstimulation method termed coined as sequential narrow-field (SNF) stimulation, that can reduce hippocampal seizures while limiting the fringing field effects that can evoke adverse responses.[2] Using the systemic kainic acid status epilepticus (KA-SE) model of temporal lobe epilepsy (TLE) in rats, the authors first compared the effects of various stimulation configurations, including open-loop wide-field (WF) stimulation, unilateral and bilateral closed-loop WF stimulation, and the newly orchestrated SNF stimulation. The SNF approach involves spatially restricted stimulus pulses delivered sequentially through the hippocampus. The results suggest bilateral closed-loop hippocampal WF stimulation significantly desynchronizes the ictal network, doubling the seizure inhibition efficacy compared to unilateral stimulation. SNF stimulation achieves comparable seizure inhibition to bilateral WF stimulation but with greater spatial precision, affecting a smaller volume of surrounding brain tissue. The reduced fringing field effects were further validated using a simulation model and motor responses in freely roaming rats during open field and place preference tests. The authors first studied various stimulation paradigms during the acute SE phase to control the timing and severity of seizures. They then addressed the caveat that acute seizures are not a human TLE-relevant model by studying the effects of SNF on chronic spontaneous recurrent seizures after SE. The authors found

closed-loop SNF stimulation achieved superior spontaneous seizure inhibition compared to the low-intensity WF stimulation. Together, this paper demonstrates that optimal seizure control with minimal off-target effects is possible via a closed-loop hippocampal SNF stimulation.

Beyond the technical innovation and clinical significance of the above findings, this study prompts new research directions that warrant further investigation. (1) Are these findings generalizable across other TLE models that directly recruit hippocampus as the seizure onset zone? The authors studied TLE using the systemic KA-SE model, where seizures likely originate in the entorhinal cortex before propagating to the hippocampus.[3] Direct hippocampal involvement could be analyzed using unilateral intrahippocampal KA and hippocampal electrical kindling models. This would also enable the investigation of SNF stimulation efficacy ipsilateral versus contralateral to the seizure initiation site. (2) Are these findings generalized across strains and species? Seizure sensitivity is highly dependent on genetic background. For example, MRI scans and postmortem histology studies suggest that the extent of neuronal damage after systemic KA-induced SE is higher in Sprague Dawley rats, the strain used in this study, compared to Wistar rats.[4] The translational potential of SNF stimulation will be greatly strengthened if its seizure inhibition effects remain consistent across various strain backgrounds. (3) Is hippocampal SNF stimulation sufficient to suppress seizures beyond the hippocampus? While this study recorded local field potentials from areas adjacent to the stimulation site, it is unclear whether hippocampal SNF stimulation also halts seizure propagation to other brain regions or reduces behavioral seizure manifestations. (4) Does hippocampal SNF stimulation affect behavioral functions directly associated with the hippocampus (e.g., spatial learning and memory) and its adjacent brain structures?

Because SNF simulation features sequentially delivered stimulation across space, the stimulation order adds a nuanced dimension to its application. The hippocampal formation is a linear structure with neuronal projection tracts oriented along the medial-lateral and dorsal-ventral planes. Therefore, it is reasonable to speculate that the seizure inhibition efficacy of SNF depends on the location and spatial order of the sequentially delivered stimulation. The current study delivered SNF from dorsal to ventral CA3, presumably along the granule cell mossy fiber track based on the coordinates. The authors investigated the necessity of sequential stimulation for SNF and found that spatially randomized stimulations failed to terminate the epileptic rhythms. However, the directionality of SNF in the spatially complex hippocampus remains largely unexplored. For example, can ventral to dorsal SNF produce better seizure inhibition? Can concurrent sequential stimulation in both hemispheres better desynchronize bilateral rhythmic activities? The efficacy of SNF directionality across the lamination of neuronal cell bodies and afferent fiber projections of hippocampus also raises intriguing questions. Would delivering SNF within or across other critical hippocampal nodes, including CA1, CA2, and DG, which "gates" the overall excitability of hippocampus, achieve similar or superior seizure inhibition compared to CA3? Systematically optimizing these factors and their stimulation parameter space holds promise for enhancing the efficacy of SNF in achieving better seizure inhibition.

Responsive neurostimulation has shown remarkable efficacy and safety in patients, suggesting long-term remodeling effects.[5] Ongoing preclinical studies are further refining neruomodulation techniquescontinue to enhance efficacy and safety while expanding their therapeutic scope. For example, Paschen et al. demonstrated that on-demand low-frequency stimulation (LFS) was almost as effective as continuous LFS in preventing hippocampal seizure clusters but with a significantly lower stimulation load.[6] However, it is noteworthy that the closed-loop approach may lack the positive effects of open-loop stimulation, which can improve overall brain stability via continuous electrical innervation.[7] Closed-loop approaches are also effective in inhibiting seizures in animal models by targeting other brain regions, like medial septum,[8] cerebellum,[9] and somatosensory cortices.[10] Beyond seizure control, on-demand rescue of sudden unexpected death in epilepsy is also proposed by delivering life-saving neurostimulation when a potentially fatal seizure is detected.[11]

The on-demand approach proves well-suited for seizure control, especially considering the unpredictable nature of discrete seizures, which can occur anywhere from less than once a year to as many as 100 times a day. Epilepsy patients with infrequent seizures often endure the side effects of the daily ASM dose, regardless of seizure occurrence. While the rate for drug-refractory epilepsy remains $\sim$30% despite the development of new ASM in the past two decades, closed-loop stimulation holds the greatest therapeutic potential for this population. Although it is challenging to directly translate mouse hippocampal SNF stimulation to humans, given large differences in brain size and anatomy, we are now closer than ever to developing a fully personalized neurostimulation treatment for TLE. The concept of SNF also sheds light on improving neurostimulation for the treatment of other neurological and psychiatric conditions like Parkinson's disease, dystonia, depression, and obsessive-compulsive disorder.

Bin Gu, PhD
Department of Neuroscience,
Ohio State University

ORCID iD

Bin Gu https://orcid.org/0000-0002-6846-5563

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

References

1. Sisterson ND, Wozny TA, Kokkinos V, Constantino A, Richardson RM. Closed-loop brain stimulation for drug-resistant epilepsy:

towards an evidence-based approach to personalized medicine. *Neurotherapeutics*. 2019;16(1):119-127.
2. Kang W, Ju C, Joo J, Lee J, Shon Y-M, Park S-M. Closed-loop direct control of seizure focus in a rodent model of temporal lobe epilepsy via localized electric fields applied sequentially. *Nature Comm*. 2022;13(1):7805. doi:10.1038/s41467-022-35540-7
3. Ben-Ari Y, Tremblay E, Riche D, Ghilini G, Naquet R. Electrographic, clinical and pathological alterations following systemic administration of kainic acid, bicuculline or pentetrazole: metabolic mapping using the deoxyglucose method with special reference to the pathology of epilepsy. *Neuroscience*. 1981;6(7):1361-1391.
4. Inostroza M, Cid E, Brotons-Mas J, et al. Hippocampal-dependent spatial memory in the water maze is preserved in an experimental model of temporal lobe epilepsy in rats. *PLoS One*. 2011;6(7): e22372.
5. Nair DR, Laxer KD, Weber PB, et al. Nine-year prospective efficacy and safety of brain-responsive neurostimulation for focal epilepsy. *Neurology*. 2020;95(9):e1244-e1256.
6. Paschen E, Kleis P, Vieira DM, et al. On-demand low-frequency stimulation for seizure control: efficacy and behavioural implications. *Brain*. 2024;147(2):505-520.
7. Paschen E, Elgueta C, Heining K, et al. Hippocampal low-frequency stimulation prevents seizure generation in a mouse model of mesial temporal lobe epilepsy. *Elife*. 2020;9:e54518.
8. Takeuchi Y, Harangozó M, Pedraza L, et al. Closed-loop stimulation of the medial septum terminates epileptic seizures. *Brain*. 2021;144(3):885-908.
9. Stieve BJ, Richner TJ, Krook-Magnuson C, Netoff TI, Krook-Magnuson E. Optimization of closed-loop electrical stimulation enables robust cerebellar-directed seizure control. *Brain*. 2023; 146(1):91-108.
10. Nelson TS, Suhr CL, Freestone DR, et al. Closed-loop seizure control with very high frequency electrical stimulation at seizure onset in the GAERS model of absence epilepsy. *Int J Neural Syst*. 2011;21(2):163-173.
11. Gu B, Adeli H. Toward automated prediction of sudden unexpected death in epilepsy. *Rev Neurosci*. 2022;33(8):877-887.