Epilepsy Currents
2024, Vol. 24(5) 370–372

DOI: 10.1177/15357597241280683
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# Closed-loop Low-frequency stimulation: seizure reduction and more

**Effect of the Closed-Loop Hippocampal Low-Frequency Stimulation on Seizure Severity, Learning, and Memory in Pilocarpine Epilepsy Rat Model**

Zare M, Rezaei M, Nazari M, Kosarmadar N, Faraz M, Barkley V, Shojaei A, Raoufy MR, Mirnajafi-Zadeh J. Effect of the closed-loop hippocampal low-frequency stimulation on seizure severity, learning, and memory in pilocarpine epilepsy rat model. *CNS Neurosci Ther.* 2024;30(3):e14656. doi:10.1111/cns.14656

Aims: In this study, the anticonvulsant action of closed-loop, low-frequency deep brain stimulation (DBS) was investigated. In addition, the changes in brain rhythms and functional connectivity of the hippocampus and prefrontal cortex were evaluated. Methods: Epilepsy was induced by pilocarpine in male Wistar rats. After the chronic phase, a tripolar electrode was implanted in the right ventral hippocampus and a monopolar electrode in medial prefrontal cortex (mPFC). Subjects' spontaneous seizure behaviors were observed in continuous video recording, while the local field potentials (LFPs) were recorded simultaneously. In addition, spatial memory was evaluated by the Barnes maze test. Results: Applying hippocampal DBS, immediately after seizure detection in epileptic animals, reduced their seizure severity and duration, and improved their performance in Barnes maze test. DBS reduced the increment in power of delta, theta, and gamma waves in pre-ictal, ictal, and post-ictal periods. Meanwhile, DBS increased the post-ictal-to-pre-ictal ratio of theta band. DBS decreased delta and increased theta coherences, and also increased the post-ictal-to-pre-ictal ratio of coherence. In addition, DBS increased the hippocampal-mPFC coupling in pre-ictal period and decreased the coupling in the ictal and post-ictal periods. Conclusion: Applying closed-loop, low-frequency DBS at seizure onset reduced seizure severity and improved memory. In addition, the changes in power, coherence, and coupling of the LFP oscillations in the hippocampus and mPFC demonstrate low-frequency DBS efficacy as an antiepileptic treatment, returning LFPs to a seemingly non-seizure state in subjects that received DBS.

## Commentary

Deep brain stimulation (DBS) is one of the newer therapies used to treat patients with pharmacoresistant epilepsy; however, the mechanisms underlying its efficacy are poorly understood. For each patient, the fundamental questions of where and how to stimulate and how often to stimulate must be addressed. Efficacy has been reported in experimental models of epilepsy and clinically using both low-frequency (LFS) and high-frequency stimulation (HFS) paradigms with only HFS approved by the US Food and Drug Administration (FDA). DBS delivered to an identified site of seizure onset such as the hippocampus or to seizure-gating networks such as the anterior thalamic nucleus has been shown to be effective.[1,2] The development and subsequent FDA approval of the Responsive Neural Stimulator (RNS®) by NeuroPace, Inc. in 2013 allows for the delivery of closed-looped DBS, where the therapeutic stimulation is delivered in response to the detection of electrographic epileptiform or seizure activity. Closed-loop stimulation is likely superior to open-loop continuous stimulation[3] with the added benefits of reduced exposure to the therapeutic stimulation accompanied by a reduced drain on the device battery. The results from an open-label long-term, multicenter treatment trial using closed-loop stimulation reported a progressive reduction in seizure rates, with the median reduction in seizure frequency increasing from 53% after 2 years to 75% after 9 years of treatment.[4,5] The most common stimulation frequency used in this trial was a high-frequency stimulus ranging from 100 to 200 Hz.[5]

Closed-loop LFS has the potential to build upon the impressive results obtained with HFS, but more data are needed. There have been numerous reports of efficacy using LFS in experimental models, but clinical evidence has been limited to case reports.[6] The highlighted basic science study was designed to test the efficacy of closed-loop LFS of the ventral hippocampus after lithium pilocarpine-induced status epilepticus (SE) in male Wistar rats.[7] The metrics evaluated were spontaneous seizure frequency and duration, spatial memory performance, and the functional connectivity between the hippocampus and the medial prefrontal cortex (mPFC) in awake

freely moving rats. Four experimental groups were examined: (1) control; (2) pilocarpine—no LFS; (3) pilocarpine + LFS; (4) no SE—only LFS. Electrodes were implanted 30–35 days after SE; a tripolar electrode was implanted in CA1 of the ventral hippocampus and a monopolar electrode was implanted in the mPFC. Spontaneous recurrent seizures (SRS) were detected by 24-h video/local field potential (LFP) recording. A program written in MATLAB was used to measure changes in LFP power for seizure detection.[8] SRS were evaluated for 3 weeks: Week 1—baseline seizure detection, Week 2—closed-loop LFS, and Week 3—post-stimulation seizure detection. The LFS consisted of 4, 200 s trains of 1 Hz, monophasic, square wave pulses, 0.1 ms pulse duration with 5 min intervals between each train. Since cognitive and memory deficits are a common comorbidity in patients with temporal lobe epilepsy[9] and in the pilocarpine model,[10] the effect of LFS on deficits in spatial learning and memory was also evaluated, with each experimental group behaviorally tested using the Barnes maze. Finally, the effect of LFS on the functional connectivity between the hippocampus and the mPFC was examined in all 4 experimental groups due to the role played by the mPFC in cognitive function.[11] The power spectra density of delta, theta, and gamma wave LFP activity in the hippocampus and mPFC was determined at three time points: pre-ictal—30 s before ictal onset; ictal—5 s after ictal onset; post-ictal—30 s after the termination of ictal discharges. Coherence across the frequency spectrum between the two regions was also calculated.

Closed-loop LFS significantly decreased SRS frequency and duration during the period of LFS with this positive effect persisting during the 7-day sampling period once therapeutic stimulation was discontinued, indicating that the LFS not only had an antiseizure effect but was also potentially disease-modifying. Deficits in learning and spatial memory also improved with LFS when assessed using the Barnes maze. Unstimulated pilocarpine-treated rats exhibited significant deficits in escape latency, total errors, and distance traveled compared to unstimulated controls. LFS reversed the deficits in these metrics to control levels. LFS also reversed deficits in search strategy, goal sector explorations, and target-seeking behavior, present in pilocarpine-treated rats, to control levels. LFS also improved the functional connectivity between the hippocampus and the mPFC in pilocarpine-treated rats. The power of delta, theta, and gamma LFP activity was significantly increased in both the hippocampus and the mPFC during all three sampling periods. LFS returned each of these to control levels. LFS stimulation also reduced hypersynchrony, as measured by increased coherence in the theta bands, between the hippocampus and mPFC.

In conclusion, the study by Zare et al. provides strong evidence that closed-loop LFS is not only antiepileptic but potentially disease-modifying. The therapeutic benefits of this stimulation were not limited to seizure reduction but extended to correcting deficits in memory and learning and the functional connectivity between the hippocampus and the mPFC. It is important to determine whether these positive results extend to other experimental models of epilepsy with the data collected over a sampling period of >1 week. However, the results support further development of closed-loop LFS as a therapy for pharmacoresistant epilepsy and could provide an alternative approach for those patients who fail to respond to HFS. In a recent, limited retrospective study, the effect of responsive LFS on seizure frequency was examined in patients with focal-resistant epilepsy previously treated with HFS.[12] In these patients, LFS resulted in a significant reduction in median seizure frequency when compared to their response to HFS and an even greater reduction when compared to baseline seizure frequency. However, in one patient, LFS resulted in an increase in median seizure frequency when compared to HFS. While these results provide strong evidence of the therapeutic potential of LFS they also highlight that the challenges of using DBS to treat epilepsy are no different from the use of antiseizure medications (ASM). The antiseizure mechanism of both HFS and LFS are not clearly understood but there is evidence that HFS results in desynchronization and depolarization block while there is evidence that LFS can induce long-term depression and hyperpolarization, with its effect lasting beyond the duration of the stimulus. Due to the limited clinical experience using LFS, it is premature to compare the efficacy of LFS to HFS. The fundamental questions of where and how to stimulate will need to be addressed in each patient.

Since LFS is not currently approved by the FDA additional efficacy and safety studies are needed to provide sufficient preclinical data to justify a clinical trial. From a translational perspective, it would be interesting to test the efficacy of DBS, independent of the stimulation frequency, in combination with different ASM. Clinically, DBS is an adjunctive therapy such that each patient continues to take ASM while receiving therapeutic stimulation. The combination of ASM taken by each patient is likely different. Therefore, moving forward it will be important to determine which ASM enhance, interfere, or have no effect on DBS efficacy.

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## Declaration of Conflicting Interests

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

## Funding

The author received no financial support for the research, authorship, and/or publication of this article.

## References

1. Fisher R, Salanova V, Witt T, et al. Electrical stimulation of the anterior nucleus of thalamus for treatment of refractory epilepsy.

*Epilepsia*. 2010;51(5):899–908. doi:10.1111/j.1528-1167.2010.02536.x
2. Li MHC, Cook MJ. Deep brain stimulation for drug-resistant epilepsy. *Epilepsia*. 2018;59:273–290. doi:10.1111/eoi.13964
3. Salam MT, Velazquez JLP, Genov R. Seizure suppression efficacy of closed-loop versus open-loop deep brain stimulation in a rodent model of epilepsy. *IEEE Trans Neural Syst Rehab Eng*. 2015;24(6):710–719. Doi: 10.1109/TNSRE.2015.2498973
4. 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. doi:10.1212/WNL.0000000000010154
5. Skarpaas TL, Jarosiewicz B, Morrell MJ. Brain-responsive neurostimulation for epilepsy (RNS® system). *Epilepsy Res*. 2019;153:68–70. doi:10.1016/j.eplepsyres.2019.02.003
6. Lim SN, Lee CY, Lee ST, et al. Low and high frequency hippocampal stimulation for drug-resistant mesial temporal lobe epilepsy. *Neuromodulation*. 2016;19:365–372. doi:10.111.ner.12435
7. Zare M, Rezaei M, Nazari M, et al. Effect of the closed-loop hippocampal low-frequency stimulation on seizure severity, learning, and memory in pilocarpine epilepsy rat model. *CNS Neurosci Ther*. 2024;30(3):e14656. doi:10.1111/cns.14656
8. Zare M, Nazari N, Shojaei A, Raoufy MR, Mirnajafi-Zadeh J. Online analysis of local field potentials for seizure detection in freely moving rats. *Iran J Basic Med Sci*. 2020;23:173–177. doi:10.22038/IJBMS.2019.38722.9183
9. Bell B, Lin JJ, Seindenberg M, Hermann B. The neurobiology of cognitive disorders in temporal lobe epilepsy. *Nat Rev Neurol*. 2011;7:154–164. doi:10.1038/nrneurol.2011.3
10. Lopes MW, Lopes SC, Santos DB, et al. Time course evaluation of behavioral impairments in the pilocarpine model of epilepsy. *Epilepsy Behav*. 2016;55:92–100. doi:10.1016/j.yebeh.2015.12.001
11. Euston DR, Gruber AJ, McNaughton BL. The role of the medial prefrontal cortex in memory and decision making. *Neuron*. 2012;76:1057–1070. doi:10.1016/j.neuron.2012.12.002
12. Alcala-Zermeno JL, Starnes K, Gregg NM, Worrell G, Lundstrom BN. Responsive neurostimulation with low-frequency stimulation. *Epilepsia*. 2023;64:e16–e22. doi:10.111/epi.17467