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BRIEF COMMUNICATION

Responsive neurostimulation with low-frequency stimulation

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Abstract

Deep brain stimulation and responsive neurostimulation (RNS) use high-frequency stimulation (HFS) per the pivotal trials and manufacturer-recommended therapy protocols. However, not all patients respond to HFS. In this retrospective case series, 10 patients implanted with the RNS System were programmed with low-frequency stimulation (LFS) to treat their seizures; nine of these patients were previously treated with HFS (100 Hz or greater). LFS was defined as frequency < 10 Hz. Burst duration was increased to at least 1000 ms. With HFS, patients had a median seizure reduction (MSR) of 13% (interquartile range [IQR] = −67 to 54) after a median of 19 months (IQR = 8–49). In contrast, LFS was associated with a 67% MSR (IQR = 13–95) when compared to HFS and 76% MSR (IQR = 43–91) when compared to baseline prior to implantation. Charge delivered per hour and pulses per day were not significantly different between HFS and LFS, although time stimulated per day was longer for LFS (228 min) than for HFS (7 min). There were no LFS-specific adverse effects reported by any of the patients. LFS could represent an alternative, effective method for delivering stimulation in focal drug-resistant epilepsy patients treated with the RNS System.

KEYWORDS

alternative parameters, low-frequency stimulation, neuromodulation, neurostimulation, responsive neurostimulation

1 | INTRODUCTION

Intracranial neurostimulation is a palliative approach for the treatment of adult patients with drug-resistant epilepsy (DRE). It involves electrical stimulation with physician-defined current, pulse width, and frequency over a determined period of time to alter neural activity at seizure foci and network nodes. There are two US Food and Drug Administration-approved intracranial stimulation modalities for focal epilepsy: anterior thalamic nucleus (ANT) deep brain stimulation and responsive neurostimulation (RNS). Both modalities are typically programmed with high-frequency stimulation (HFS) as used in the pivotal trials.[1,2] For this study, we consider stimulation of 100 Hz or greater as HFS, consistent with prior observations.[3] The RNS System is a closed loop system that detects and records intracranial epileptiform activity arising from seizure foci and/or network nodes and stimulates automatically according to physician-programmed settings. One therapy is comprised of two programmable bursts and can be repeated up to five times if the abnormal electrical activity

continues, although only the first delivered therapy is counted by the RNS System. The recommended initial stimulation settings are frequency of 200 Hz (or pulses per second), pulse width of 160 μs, and burst duration of 100 ms. These parameters have been informed in part by the experience of long-term treatment trials that resulted in a 75% median seizure reduction at 9 years.[4]

Low-frequency stimulation (LFS) has been studied in animals as a potential antiepileptic strategy specially in rodent kindling models. In humans, LFS has been studied in DRE patients through stimulation of a wide variety of targets including hippocampus,[5] fornix,[6] thalamus,[7] and cortex.[8] Regarding the latter, chronic subthreshold stimulation involves open-loop, continuous electrical stimulation of seizure foci in focal DRE patients through LFS and may be particularly useful when stimulating eloquent cortex.[9] However, LFS for intracranial stimulation is not often considered, in part due to concerns that it may even worsen seizures.[3] To our knowledge, a within-patient comparison of HFS and LFS for implanted intracranial stimulation devices has not been published.

In this report, we aimed to evaluate the clinical response of patients treated the RNS System programmed with LFS. We suggest that when patients do not respond to the HFS of standard RNS settings, a lower stimulation frequency in addition to longer burst duration (LFS) are reasonable stimulation parameters to consider.

2 | MATERIALS AND METHODS

This institutional review board-approved retrospective case series included all DRE patients implanted with the RNS System followed at our center with active LFS at last clinical follow-up. All variables, including clinical seizure frequency, were obtained through the electronic health record. The RNS System implantation was performed as part of clinical care.[2] HFS has been defined as stimulation of >45 Hz elsewhere.[3] We defined LFS as a stimulation frequency of <10 Hz and used a burst duration of 5 s. We chose the 7-Hz theta frequency, which we have used previously, given its association with the limbic system.[10–12] Pulse width was 160 μs, except for Patient 5 during HFS, when it was 240 μs. Specifically, stimulation was typically 5-s trains of 35 biphasic pulses with phase width of 160 μs. Stimulation amplitude was adjusted using charge density as the relevant metric, per typical clinical practice. Electrocorticographic (ECoG) events were not analyzed, as detection parameters were changed during clinical care, precluding direct comparisons over time. Responder rate was defined as clinical seizure frequency reduction of ≥50%. We determined total time of stimulation per day, reported in minutes per day; pulses delivered per day, reported as pulses in a 24-h period; and calculated charge delivered per hour, reported as millicoulombs (mC) per hour:

$$\frac{Current(mA) \times Pulse\ Width(s) \times Frequency(Hz) \times Burst\ Duration(s) \times 1.27 \times Therapies\ Delivered\ per\ Day}{24\ h/day}.$$

Because the RNS System has two programmable bursts per therapy, when the same lead was used for both Burst 1 and Burst 2, the charges were added. When burst settings were different, the burst providing the largest charge was used. The 1.27 factor represents the average number of therapy repetitions delivered until the sensed abnormal electrical activity was no longer detected.

All statistics and graphs were performed in Prism version 9.3.1 for Windows (GraphPad Software). Continuous and categorical variables are described as median with interquartile range (IQR) and percentage, respectively. Chi-squared and Fisher exact tests were used for comparison of proportions and frequencies. Mann–Whitney *U* or Wilcoxon signed-rank tests were used for median comparison between groups as appropriate. Spearman rho was used for correlation analysis. Probability values ≤ .05 were considered statistically significant. Deidentified data are available upon request.

3 | RESULTS

A total of 39 patients implanted with the RNS System were followed at our center between August 2004 and April 2022, and 10 patients were included in our analysis. Two patients were programmed with LFS in the past but were not on LFS at last clinical follow-up; one was implanted at an outside center, trialed on LFS in our clinic for <3 months, and then programmed back to HFS by their primary neurologist. The other patient was on a mixed HFS and LFS protocol at last follow-up. Eleven patients were on LFS at last clinical follow-up. One of these patients was excluded due to unreliable clinical seizure reporting. Of the remaining 10 patients, one patient was initially started on LFS and has never been on HFS; this patient received promising LFS via temporary trial stimulation during stereoelectroencephalographic evaluation.[9,13] Table 1 summarizes patient baseline characteristics and seizure frequencies.

Median seizure frequency at baseline prior to RNS System implantation was 6 seizures per month (sz/mo; IQR = 4–8). After a median of 19 months (IQR = 8–49)

TABLE 1 Baseline characteristics

Patient #	Sex/age at implant, years	Seizure onset/ type of EEG	MRI findings	Electrode location, orientation, and type	ASDs trialed before RNS, *n*/ASDs at time of implant	ASDs at last follow-up	Baseline seizure Fq, sz/month	Seizure Fq at last HFS, sz/ month	Seizure Fq at last LFS, sz/month	Follow-up time, month	LFS time, month	Comments
1	F/27	Left temporal/ subdural electrode	Post left ATL with residual MTS	Left temporal neocortex, subdural	5/FBM, LEV, LTG	FBM, LEV, LTG	4.5	3	1	206	37	
2	M/49	Bilateral temporal/ SEEG	Nonlesional MRI	Bilateral mesial temporal, longitudinal depths	5/LTG	LTG	6	10	7.5	65	6	Implanted at different center. Orthogonal bitemporal leads replaced with longitudinal leads.
3	F/23	Bilateral temporal/ SEEG	Right hippocampal atrophy, left MTS	Bilateral mesial temporal, longitudinal depths	8/CBZ, CLB, CZP	CLB, CNB	6	10	3	61	14	
4	F/31	Bilateral temporal/ scalp EEG	Nonlesional MRI	Bilateral mesial temporal, longitudinal depths	2/PRP, LTG	CLB, LEV, OXC	6	1.5	0	51	6	Implanted at different center. Switched to LFS at our center.
5	F/37	Left temporal/ scalp EEG	Bilateral MTS	Bilateral mesial temporal, longitudinal depths	2/ECBZ, LCM	BRV, CLB, CNB, LEV	12	30	3	47	35	Infection with initial device leading to explant, subsequently reimplanted.
6	F/37	Bilateral temporal/ scalp EEG	Bilateral MTS	Bilateral mesial temporal, longitudinal depths	9/GBP, LCM, LEV	GBP, LCM, LEV	4	3.5	2	29	10	Patient underwent left temporal LITT as 95% of ECoG detections were left-sided.
7	F/21	Left temporal/ SEEG	Nonlesional MRI	Left hippocampal and parahippocampal areas, longitudinal depths	4/LEV	LEV	6	4.6	4.6	22	2	Patient committed suicide, known MDD.
8	M/49	Bilateral temporal/ scalp EEG	Right MTS	Bilateral mesial temporal, longitudinal depths	4/CBZ, LCM, LEV, LZP	CBZ, LCM, LEV, LTG	3.5	.25	.5	22	14	
9	F/53	Left frontal/ SEEG	Left frontal FCD	Left frontal FCD, orthogonal depths	3/LCM, OXC, TPM	LCM, OXC, TPM	16	NA	2	26	26	Patient on LFS since implant.
10	M/18	Bilateral temporal/ scalp EEG	Left temporal encephalocele s/p resection	Bilateral mesial temporal, longitudinal depths	6/LCM, LTG	BRV, LCM	3	4	0	9	4	

Abbreviations: ASD, antiseizure drug; ATL, anterior temporal lobectomy; BRV, brivaracetam; CBZ, carbamazepine; CLB, clobazam; CNB, cenobamate; CZP, clonazepam; ECBZ, eslicarbazepine; ECoG, electrocorticography; EEG, electroencephalography; F, female; FBM, felbamate; FCD, focal cortical dysplasia; Fq, frequency; GBP, gabapentin; HFS, high-frequency stimulation; LCM, lacosamide; LEV, levetiracetam; LFS, low-frequency stimulation; LITT, laser interstitial thermal therapy; LTG, lamotrigine; LZP, lorazepam; M, male; MDD, major depressive disorder; MRI, magnetic resonance imaging; MTS, mesial temporal sclerosis; NA, not applicable; OXC, oxcarbazepine; PRP, perampanel; RNS, responsive neurostimulation; SEEG, stereoelectroencephalography; s/p, status post; sz, seizures; TPM, topiramate.

on HFS, patients ($n = 9$) had a median seizure reduction (MSR) of 13% (IQR = −67 to 54). Seizure frequency after HFS was not significantly different compared to baseline (4 sz/mo, IQR = 2–10 vs. 6 sz/mo, IQR = 4–8; $p = .88$). Patients were on LFS for a median of 12 months (IQR = 5–28). With LFS, patients had significantly fewer seizures (2 sz/mo, IQR = .4–3) compared to HFS (4 sz/mo, IQR = 2–10; $p = .02$) and baseline (6 sz/mo, IQR = 4–8; $p = .006$). The MSR associated with LFS when compared to baseline and HFS was 76% (IQR = 43–91) and 67% (IQR = 13–95), respectively. LFS had an 80% responder rate compared to baseline, and a 56% responder rate compared to HFS (Figure 1). When compared to baseline, LFS had a significantly higher proportion of responders than HFS (80% vs. 22%, $p = .02$).

Charge density and charge per hour were not significantly different between HFS and LFS (2.0 μC/cm^2, range = .5–4.6 vs. 3 μC/cm^2, range = 1.0–5.5; $p = .07$ and .5 mC/h, range = .004–3.4 vs. 4.4 mC/h, range = .02–24.5; $p = .2$, respectively). Time stimulated per day was significantly longer with LFS (228 min, range = 2–717) compared to HFS (7 min, range = .4–27; $p = .006$). Pulses per day were not significantly different between HFS and LFS (76 302 pulses, range = 2489–161 442 vs. 97 451 pulses, range = 1037–306 578; $p = .8$). Therapies delivered per day (tpd) were not significantly different between HFS and LFS (1502 tpd, IQR = 298–2519 vs. 1254 tpd, IQR = 151–1978; $p = .7$). Figure 1E shows a long episode ECoG recording from a patient treated with LFS. Typically, 30 s of detected abnormal activity are required to trigger the storage of a long episode (long episode length). Here, the long episode length was increased from 30 s to 60 s, as LFS can provide up to 50 s of stimulation per therapy (if two bursts of 5 s are repeated five times). Additionally, the length of the capture window was increased from 90 s to 180 s. The capture window is divided such that two thirds is reserved for pretrigger activity (including the abnormal activity required to trigger the long episode storage), and one third

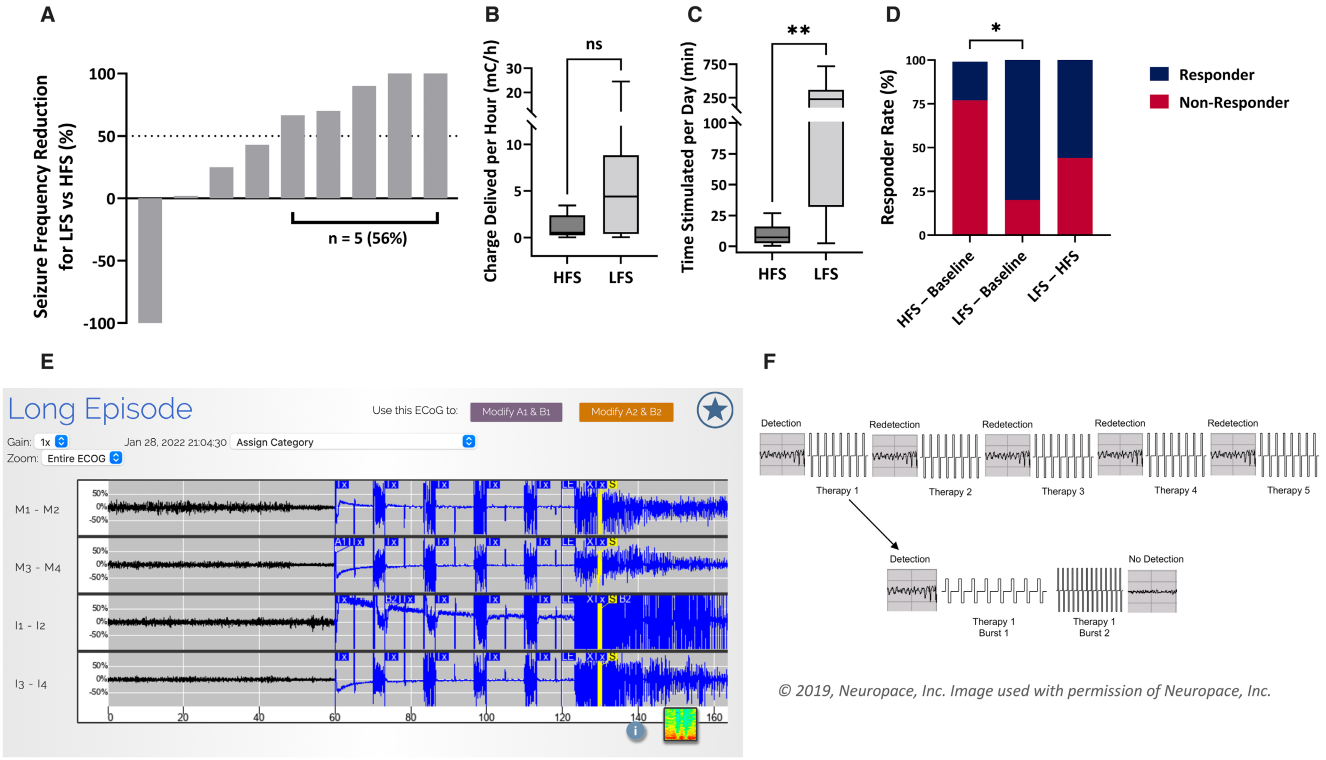

FIGURE 1 (A) Individual seizure frequency reduction after low-frequency stimulation (LFS) compared to high-frequency stimulation (HFS; $n = 9$) from worst (lower left) to best (upper right). The patient who had increased seizure frequency after LFS (first bar) is still a responder compared to baseline (Patient 8; see Table 1). (B) Comparison of median charge delivered per hour ($p = .2$). (C) Comparison of time stimulated per day ($p = .006$). (D) Percentage of responders after HFS from baseline, after LFS from HFS, and after LFS from baseline, respectively. LFS had a significantly higher proportion of responders than HFS (80% vs. 22%, $p = .02$). (E) Visualization of an electrocorticographic (ECoG) long episode with LFS after adjusting the ECoG capture window from 90 s to 180 s and increasing the long episode length to 60 s. In this example, Burst 1 and Burst 2 are set to 5 s, that is, up to 50 s of stimulation total can be delivered per therapy. (F) Graphic representation of a therapy that can be repeated up to five times as long as abnormal activity is detected by the programmed detection settings; each therapy is made from two separate programmable bursts. Only the first delivered therapy is counted by the system to obtain the average number of therapies per day. *$p < .05$, **$p < .01$. ns, not significant.

for posttrigger activity.[14] Thus, with a 60-s long episode length, increasing the capture window to 180 s allows for 60 s to be recorded before the 60-s long episode and 60 s of posttrigger activity.[14] Table 2 shows the HFS and LFS parameters used for each patient. There were no LFS-specific adverse effects reported in any of the patients.

4 | DISCUSSION

In this study of 10 DRE patients treated with the RNS System for predominantly bitemporal mesial epilepsy, LFS was an effective approach to improve seizure control after using standard HFS settings. The time of stimulation per day was significantly longer with LFS than HFS. No adverse events related to LFS were reported. These results suggest that LFS coupled with longer stimulation times may be effective for cortical intracranial stimulation.

In our study, we coupled LFS with longer burst durations, effectively increasing the time of stimulation per day while maintaining the total amount of charge delivered. In other words, stimulation was delivered over a longer period of time, but there was not a significant difference in the charge delivered per hour; thus, we do not expect that LFS will have any significant negative impact on battery longevity (although this has not been verified). The number of therapies delivered per day was not significantly different between HFS and LFS, suggesting that a change in delivered pulses did not lead to the benefit associated with LFS. Similarly, pulses per day were also comparable between HFS and LFS. The benefit of LFS may be from increased stimulation time, lower stimulation frequency, or a combination of the two. Previous reports suggest that for some anatomical structures, LFS may provide a greater[6] or lesser[15] benefit than HFS, which suggests the ideal stimulation frequency may depend on stimulation location. Another possibility is that some patients benefit from lower stimulation frequencies due to characteristics of their epileptic networks.[5,16]

A concern regarding the use of LFS is the possibility of seizure exacerbation. However, there is evidence suggesting potential benefit from LFS in mesial temporal epilepsy,[17] similar to most patients in this study. LFS during invasive epilepsy monitoring has been used for seizure induction to facilitate epileptogenic zone identification, although higher frequencies (e.g., 50 Hz) have been noted to induce seizures more readily.[18] Chronic LFS of cortical structures has been safe and effective in epilepsy patients with predominantly eloquent seizure onset zones.[9] Seizure induction through transcranial magnetic stimulation (TMS) has been a safety concern, typically for frequencies of 10 Hz or greater,[19] although mechanisms underlying TMS differ significantly from invasive neurostimulation, making comparisons

TABLE 2 Stimulation parameters

Patient	Frequency, Hz		Charge density, μC/cm²		Burst duration, ms		Therapies delivered per day		Charge, mC/h		Time stimulated, min/day		Pulses per day		Duration of stimulation, months	
	HFS	LFS	HFS	LFS	HFS	LFS	HFS	LFS	HFS	LFS	HFS	LFS	HFS	LFS	HFS	LFS
1	333	7	2.5	4.5	200	5000	100	191	.3	.5	.8	40.4	16 916	17 223	169	37
2	100	7	2	2.5	200	5000	1502	1316	.5	7.9	12.7	278.6	76 302	118 664	59	6
3	150	7	3.5	3	100	5000	3869	3400	3.4	24.5	16.4	719.7	147 409	306 578	46	14
4	100	7	4.6	4.6	100	5000	1266	604	.5	.8	5.4	65.2	32 156	27 776	45	6
5	200	7	1	5.5	100	5000	1723	2087	.9	6.8	7.3	441.7	87 528	188 185	11	35
6	100	7	2	3	200	5000	495	23	.2	.02	4.2	2.4	25 146	1037	18	10
7	100	7	2.5	2.5	200	5000	1860	1191	3.1	7.2	15.7	252.1	94 488	10 739	19	2
8	100	7	1.5	3	200	5000	3178	1618	1.6	11.7	26.9	342.5	161 442	145 895	8	14
9	NA	7	NA	3.5	NA	5000	NA	1941	NA	2.0	NA	205.4	NA	87 510	NA	26
10	100	7	.5	1	200	5000	49	32	.004	.04	.4	6.8	2489	2885	5	4

Note: Pulse width was 160 μs for all patients when on HFS except for Patient 5, for whom it was 240 μs. Pulse width was 160 μs for all patients when on LFS. HFS values represent parameters for Burst 1, which are the same for Burst 2 except for Patients 3 and 4. LFS values represent parameters for Burst 1, which are the same for Burst 2 except for Patients 4, 6, and 9.

Abbreviations: C, coulomb; HFS, high-frequency stimulation; LFS, low-frequency stimulation; NA, not applicable.

difficult. For subcortical structures, the seizure exacerbation potential from invasive neurostimulation previously reported by Velasco et al. is restricted to bilateral, high-voltage centromedian nucleus thalamic deep brain stimulation (6 Hz, 30 V) in generalized epilepsy with absence seizures.[20] Other seizure types, including generalized onset, have been treated with thalamic LFS without reported adverse effects.[11] Prior work suggests that ANT stimulation at 15–45 Hz may increase synchronization between hippocampus and ANT.[3] We excluded one patient stimulated with 40 Hz, who noted an 82% seizure reduction compared to baseline and 53% seizure reduction compared to HFS (100 Hz) without side effects from stimulation.

One concern of LFS is of a more technical nature; increasing the burst duration increases the blanking duration of the amplifier to reduce artifact, making the electrographic activity during the seizure more difficult to visualize in the recorded ECoGs. This can be ameliorated by increasing the long episode length such that it is greater than the maximum therapy time (e.g., at least 50 s if two bursts of 5 s are each delivered five times) to record only ECoGs of interest. In addition, the capture window can be increased, for example, from 90 s to 180 s, to store more useful ECoGs (see Figure 1E). Our study is limited by its retrospective nature, which carries risks of inconsistencies related to data documentation in the electronic health record, lack of randomized control data and matched cohorts, and selection biases.

In conclusion, although HFS is generally effective in DRE patients treated with the RNS System, LFS offers a viable alternative approach and may be a beneficial RNS programming approach for patients who have not responded to standard high-frequency settings. Other studies demonstrate that cortical[9] and thalamic[21] LFS can be effective; thus, LFS as well as HFS may be effective for reducing seizure frequency.

AUTHOR CONTRIBUTIONS

J.L.A.-Z. reviewed the medical records, performed the statistical analyses, and wrote the initial draft. B.N.L. participated in all aspects of the work and provided supervision. All authors contributed to conception of the work or data acquisition, critically revised the manuscript, and approved the final version.

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CONFLICT OF INTEREST

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