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RESEARCH ARTICLE

Centromedian region thalamic responsive neurostimulation mitigates idiopathic generalized and multifocal epilepsy with focal to bilateral tonic–clonic seizures

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Abstract

Objective: Although >30% of epilepsy patients have drug-resistant epilepsy (DRE), typically those with generalized or multifocal disease have not traditionally been considered surgical candidates. Responsive neurostimulation (RNS) of the centromedian (CM) region of the thalamus now appears to be a promising therapeutic option for this patient population. We present outcomes following CM RNS for 13 patients with idiopathic generalized epilepsy (IGE) and eight with multifocal onsets that rapidly generalize to bilateral tonic–clonic (focal to bilateral tonic–clonic [FBTC]) seizures.

Methods: A retrospective review of all patients undergoing bilateral CM RNS by the senior author through July 2022 were reviewed. Electrodes were localized and volumes of tissue activation were modeled in Lead-DBS. Changes in patient seizure frequency were extracted from electronic medical records.

Results: Twenty-one patients with DRE underwent bilateral CM RNS implantation. For 17 patients with at least 1 year of postimplantation follow-up, average seizure reduction from preoperative baseline was 82.6% (SD = 19.0%, median = 91.7%), with 18% of patients Engel class 1, 29% Engel class 2, 53% Engel class 3, and 0% Engel class 4. There was a trend for average seizure reduction to be greater for patients with nonlesional FBTC seizures than for other patients. For patients achieving at least Engel class 3 outcome, median time to worthwhile seizure reduction was 203.5 days (interquartile range = 110.5–343.75 days). Patients with IGE with myoclonic seizures had a significantly shorter time to worthwhile seizure reduction than other patients. The surgical targeting strategy evolved after the first four subjects to achieve greater anatomic accuracy.

Significance: Patients with both primary and rapidly generalized epilepsy who underwent CM RNS experienced substantial seizure relief. Subsets of these

patient populations may particularly benefit from CM RNS. The refinement of lead targeting, tuning of RNS system parameters, and patient selection are ongoing areas of investigation.

KEYWORDS
generalized epilepsy, neuromodulation, RNS therapy, surgery, thalamus

1 | INTRODUCTION

Epilepsy is estimated to affect 70 million people worldwide,[1] with an estimated >30% meeting criteria for intractable and drug-resistant disease according to the specifications of the International League Against Epilepsy (ILAE).[2] Drug-resistant epilepsy (DRE) bears a steep cost to patients' quality of life and is associated with high levels of morbidity and mortality, including a higher rate of sudden unexpected death in epilepsy.[3] Although epilepsy surgery is central to the management of DRE, millions of patients worldwide have not been considered to be surgical candidates because their seizures have multifocal or generalized onsets.

Deep brain stimulation (DBS) was introduced in the 1950s as a viable modality for treating epilepsy.[4] Based in part on studies demonstrating the capacity of stimulation of the centromedian (CM) nucleus of the thalamus to desynchronize cortical electroencephalographic (EEG) signals in cats,[5] Velasco et al. began performing CM DBS for a series of generalized and multifocal epilepsy patients and published reports of their outcomes beginning in 1987.[6] Initial attempts to replicate their results were not successful, possibly because of inconsistencies in patient selection and stereotactic targeting and possibly because of small sample sizes.[7,8] Nonetheless, subsequent trials and case reports have supported the effectiveness of CM DBS, particularly for generalized epilepsy.[9–11]

The NeuroPace responsive neurostimulation (RNS) system is a closed-loop alternative to DBS, in which stimulation is triggered by neural activity specified in programmable detection settings.[13] We previously reported an initial series of four idiopathic generalized epilepsy (IGE) patients undergoing CM RNS who obtained substantial reductions in seizure frequency and severity.[12] Case reports and short series have also suggested the utility of bithalamic RNS for multifocal epilepsy, with >50% reduction in seizure frequency in all reported cases.[13,14] These reports have demonstrated the promise of CM RNS in difficult-to-treat generalized epilepsies, leading to the ongoing multicenter NAUTILUS trial of CM RNS for IGE (ClinicalTrials.gov: NCT05147571) and the RNS System LGS Feasibility Study (ClinicalTrials.gov: NCT05339126).

Key points

- CM RNS appears effective for IGE and multifocal onset FBTC seizures, with mean seizure frequency reduction of 82.6% (SD = 19.0%, median = 91.7%) among patients with at least 1 year of postimplantation follow-up.
- Seizure types respond variably to CM RNS; the greatest seizure reduction was seen in postencephalitic epilepsy and the fastest response in myoclonic IGE, although subgroup analyses were limited by sample size.
- Reductions in long episodes were significantly associated with reductions in reported seizure frequency reduction for patients with IGE but not multifocal onset FBTC seizures.
- Direct targeting of the CM region might facilitate more specific stimulation of the CM region, although clinical implications are unclear.
- Further work is ongoing to optimize CM RNS targeting, parameter tuning, and patient selection.

Here, we report the outcomes and targeting methodology in 21 patients undergoing CM RNS for drug-resistant IGE or multifocal onset focal to bilateral tonic–clonic (FBTC) seizures.

2 | MATERIALS AND METHODS

2.1 | Patient selection

A retrospective review of an institutional review board (IRB)-exempt epilepsy surgery registry identified all patients who underwent bilateral RNS implantation targeting the CM region by a single surgeon between March 2018 and July 2022. No patients were enrolled in a clinical trial of RNS implantation for epilepsy. RNS implantation was performed on the recommendation of a multidisciplinary surgical epilepsy conference. Preoperative insurance authorization was obtained for all surgical procedures.

2.2 | Surgical procedure

Bilateral implantation of two 4-contact depth leads (contact length = 2.0 m, intercontact interval = 1.5 mm; DL330-3.5, NeuroPace) was performed under general anesthesia using robotic stereotactic assistance (ROSA, Zimmer Biomet). Patients were positioned supine for transfrontal entry points (except for one patient who underwent transparietal approach) with head fixation via a Leksell frame and coregistration performed using fiducial points selected on the computed tomography-based reconstruction of the frame pins.

Indirect targeting of the CM region was performed in the first four implanted patients using Schaltenbrand atlas coordinates ±10 mm lateral, 1 mm anterior, 1 mm superior to the anterior–posterior commissural (AC-PC) midpoint, as described in previous case series.[7,15] Direct targeting of the CM region was performed in subsequent patients using direct visualization based on a magnetization-prepared two rapid acquisition gradient echoes (MP2RAGE) sequence[16] with initial indirect coordinates of ±8 mm lateral, 10–11 mm posterior, and 0 mm superior. Entry points were adjacent to the coronal suture, and trajectories did not traverse the ventricle. Adjustments were made to the target and trajectory after viewing the imaging planes 3–4 mm above the target plane (Figure 1)

2.3 | Seizure outcomes

Clinical outcomes were retrospectively collected from the electronic medical record. Extracted data points from follow-up visits included percent reduction from preoperative baseline of primary seizure frequency (with 100% designating seizure freedom and 0% designating no change in seizures), Engel classification,[17] ILAE classification of epilepsy surgery outcome,[18] and antiseizure medication regimen.

Percent seizure frequency reduction at last follow-up was compared between each patient group and the remainder of patients using two-tailed *t*-tests including all patients with at least 1 year of follow-up after RNS implantation. For patients who achieved a worthwhile reduction in seizures, time to worthwhile reduction was compared between each patient group and the remainder of patients using Cox proportional hazard analysis.

2.4 | Device recordings

2.4.1 | Detection and stimulation settings

Intracranial EEG was recorded using a Surface Area detector (which calculates the area beneath the curve of the electrographic tracing) with default settings and without stimulation for an initial period, as per NeuroPace guidelines, to capture baseline electrophysiology to inform patient-specific detector and stimulation settings. Bandpass detectors to detect low-frequency thalamic activity and low-dose bipolar stimulation then typically were enabled (for five patients, line length detectors, which calculate the length of electrographic tracing thereby tracking frequency and amplitude, were also used prior to enabling stimulation). These detector and stimulation parameters were tuned subsequently to maximize detection sensitivity and specificity, minimize acute stimulation side effects, and lessen the occurrence of clinical seizures and long episodes, the latter of which is used as a proxy for electrographic seizures. Detection and stimulation settings were compared between seizure type groups using χ^2, analysis of variance, and two-tailed *t*-tests.

2.4.2 | Effects of RNS over time

To control for state static and time-varying confounders, the treatment effect of charge density (a standard measure of stimulation quantity) on seizure reduction was measured using a marginal structural model with stabilized inverse proportion treatment weighting truncated at 5%, with patients grouped as >1.0 microcoulombs (μC)/cm^2, ≥1.0 μC/cm^2 and < 2.0 μC/cm^2, ≥2.0 μC/cm^2 and < 3.0 μC/cm^2, and ≥3.0 μC/cm.[19] Fitting oscillations and one over f (FOOOF) spectral analysis, which adjusts for the aperiodic component and provides a dominant central frequency value, using chronic RNS intracranial EEG of the 5 s immediately preceding stimulation to characterize the electrophysiologic state of a given thalamic nucleus at the time of stimulation.[20] Time to response (defined as ≥50% seizure reduction) was measured using a Cox proportional hazard model with inverse proportion treatment weighting to control for different seizure types. For both analyses, the start point was the day stimulation was enabled and the end point was 1 year after stimulation was enabled. Patients were included only if they had at least 52 weeks of poststimulation follow-up, and all variables were averaged across 1-week nonoverlapping windows. In the case of missing data, the last observation was carried forward.

2.4.3 | Long episode detections and patient-reported seizure reduction

The number of stimulations and long episodes were tabulated for each patient using the daily detection counter data. Piecewise regression was performed on daily long episode counts over time, split between patients'

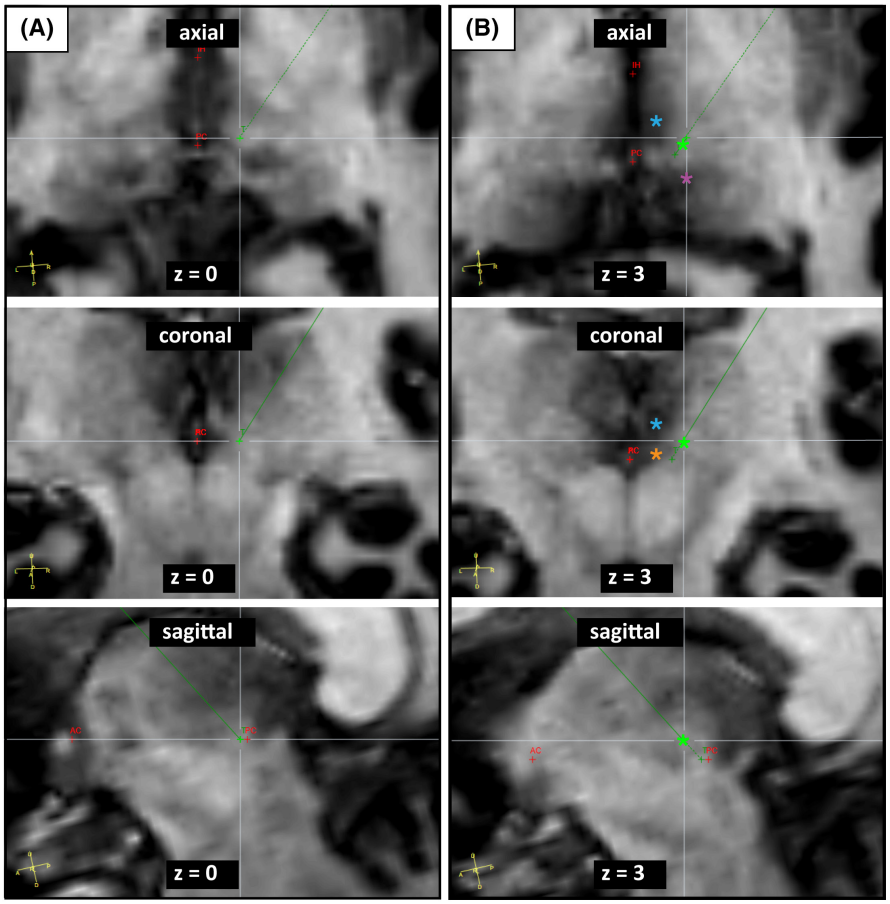


FIGURE 1 Stereotactic targeting. The targeting goal was to have the trajectory traverse the center of the centromedian region (CM) in the planes where it is most visible on an magnetization-prepared two rapid acquisition gradient echoes sequence, approximately 3 mm superior and 6 mm anterior to the posterior commissure (PC). Indirect targeting (±8, −10/11, 0, relative to the midcommissural point) was used for setting a target for the bottom of the most distal responsive neurostimulation contact (A). The views in the planning software are then advanced along this trajectory to the imaging planes ~3 mm superior to the PC. Direct targeting then proceeds by adjusting the target point until the trajectory traverses the center of the CM in this plane (B; green asterisks = CM, blue asterisks = mediodorsal nucleus, orange asterisk = parafascicular nucleus, purple asterisk = pulvinar).

detection programming epochs.[12] The average slope of these piecewise regressions, weighted by programming epoch length, was calculated for each patient. These average slopes, representing patients' average changes in long episodes over time, were tested for correlation with reported percent seizure frequency reduction at time point of last available device recording using Pearson correlation tests in patients with multifocal onset FBTC seizures and those with IGE with at least 1 year of follow-up data.

2.5 | Imaging analysis

2.5.1 | Electrode localization and volume tissue activation

RNS electrodes were localized using Lead-DBS (http://www.lead-dbs.org)[21] and Advanced Normalization Tools (http://stnava.github.io/ANTs/).[22,23] Patient-specific stimulation parameters were used to calculate volumes of tissue activation (VTAs) with a finite element method approach using standard anisotropic conductivity values for gray (σ=.33 S/m) and white matter (σ=.14 S/m) with an electric field threshold calculated using the ApproXON heuristic for VTA estimation.[21,24] To facilitate comparisons, all RNS electrodes were transformed to MNI152 ICBM 2009b NLIN asymmetric standard space using the Lead-Group toolbox,[25] and group level visualization was performed on the 7-T 100-μm ex vivo brain template.[26] (Figure 2)

Volumes of overlap between patient VTAs and Thalamus Optimized Multi Atlas Segmentation (THOMAS) atlas-based thalamic nuclei were calculated in standard space.[27] The percent of patients' VTAs overlapping with the CM region was compared between the direct and indirect targeting methods by two-tailed *t*-test. The percent of VTAs overlapping with the CM

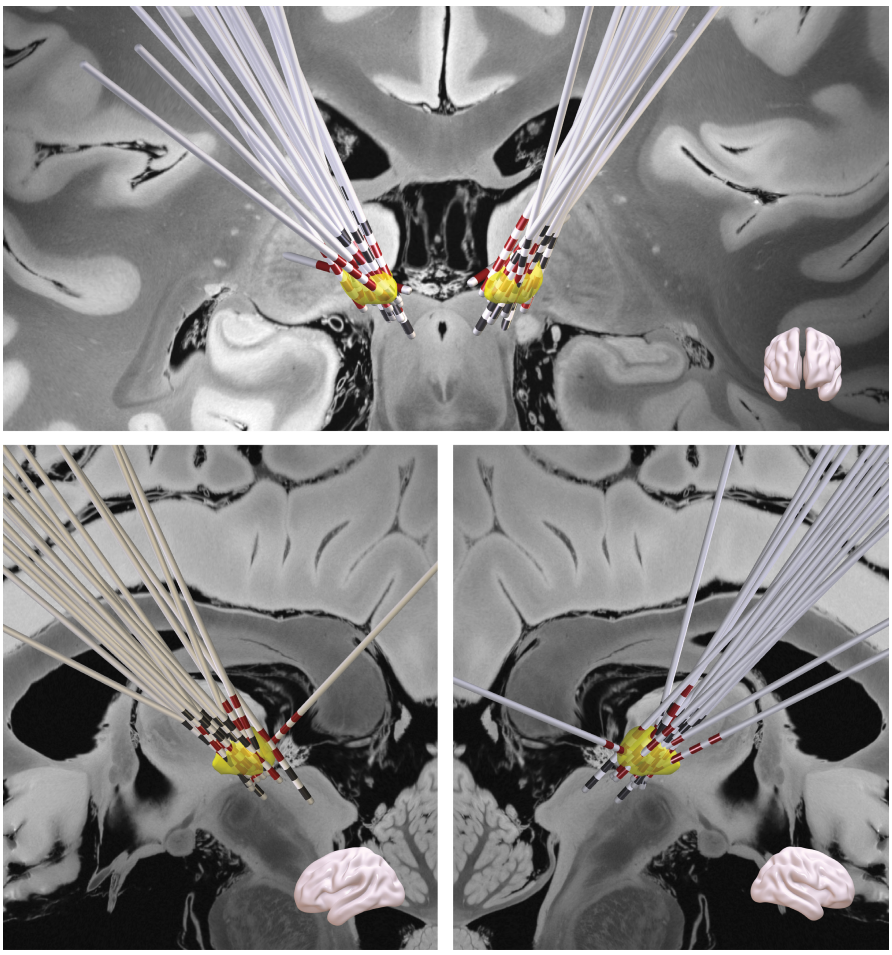


FIGURE 2 Localizations of all implanted electrodes. Red electrode contacts represent contacts with active stimulation, and the yellow regions represent the Thalamus Optimized Multi Atlas Segmentation atlas definition of the centromedian region. Brain orientation is depicted by the schematic at the bottom right of each panel. Notably, the patient with the distinctive trajectory is Patient 19, and this patient's posterior trajectory was implemented due to pulvinar involvement in seizures on stereoelectroencephalography.

region was also tested for association with seizure frequency at last follow-up using Pearson correlation for all patients with at least 1 year of follow-up after RNS implantation. The standard space Montreal Neurological Institute (MNI) coordinates of patients' distal contacts, which corresponded to target point during implantation, were compared between indirectly and directly targeted electrodes by two-tailed *t*-tests, with all contacts mirrored to the right hemisphere.

3 | RESULTS

Twenty-one total consecutive patients having bilateral CM RNS implantation were identified, all of whom had DRE and a diagnosis of IGE or multifocal onset FBTC seizures (as determined by phase 1 or phase 2 presurgical epilepsy evaluation; Tables 1 and S1). Thirteen had a diagnosis of IGE (three patients with myoclonic seizures, three tonic–clonic, and seven absence), and eight had multifocal onset FBTC seizures (four with malformations of cortical development (MCD) and four with nonlesional imaging). Of the patients with nonlesional multifocal onset FBTC seizures, three had postencephalitic epilepsy, and the other had focal epilepsy of unknown etiology found to be multifocal by stereo-electroencephalographic (SEEG) investigation. Patient age at RNS implantation ranged from 10.9 years to 42.9 years (mean = 22.2 years, SD = 8.2 years); 14 were female, and seven were male; all were English speaking. Time of last clinical follow-up ranged from 189 days to 1606 days after RNS implantation (mean = 713 days, SD = 332 days). One patient's system was explanted after 5 months due to infection. There were no other surgical complications.

3.1 | Seizure reduction

For the 17 patients with at least 1 year of postimplantation follow-up, average percent reduction from preoperative baseline of primary seizure frequency was 82.6% (SD = 19.0%, median = 91.7%; Figure 3). Of these patients, at last follow-up, three patients were Engel class 1, five Engel class 2, and nine Engel class 3 (Table 1, Figure 3B); one was ILAE class 1, one ILAE class 2, three ILAE class 3, and 12 ILAE class 4 (Table 1, Figure 3B). There was a trend for average seizure reduction to be greater for

TABLE 1 Patient characteristics before and after RNS implantation.

Patient	Age at RNS implantation, years	Primary seizure type	Epilepsy type	Etiology	MRFU, months	Clinical data at MRFU			Antiepileptic medications			% of days with RNS data downloaded
						% seizure frequency reduction	Engel class	ILAE class	Trialed	Pre-RNS	MRFU	
1	18	Absence with eyelid myoclonia	IGE	Presumed genetic	37.8	100.0%	1a	1	6	2	0	57.9%
2	22	GTC	IGE	Presumed genetic	31.7	91.7%	2b	3	9	4	2	99.2%
3	21	Myoclonic	IGE	Presumed genetic	52.7	82.5%	3a	4	5	2	1	88.3%
4	31	Absence	IGE	Presumed genetic	29.6	99.0%	1c	5	3	1	1	99.0%
5	32	Absence	IGE	Presumed genetic	29.1	62.5%	3a	4	7	2	2	91.4%
6	30	Absence	IGE	Presumed genetic	16.6	53.8%	3a	4	5	3	3	86.3%
7	27	FBTC	Multifocal	MCD	16.6	100.0%	1a	3	7	4	4	99.8%
8	31	FBTC	Multifocal	MCD	30.7	50.0%	3a	4	9	4	4	100.0%
9	18	FBTC	Multifocal	MCD	23.5	66.7%	3a	4	9	3	3	100.0%
10	20	FBTC	Multifocal	Postencephalitic	25.6	95.8%	2b	2	6	2	2	95.8%
11	25	FBTC	Multifocal	Postencephalitic	24.1	85.7%	3a	4	8	4	4	98.8%
12	13	Absence	IGE	Presumed genetic	27.9	100.0%	3a	4	8	3	3	98.6%
13	11	FBTC	Multifocal	Postencephalitic	19.7	100.0%	2d	4	2	4	4	57.5%
14	43	Absence	IGE	Presumed genetic	21.1	99.0%	2b	3	8	2	1	79.3%
15	13	Myoclonic	IGE	Presumed genetic	18.3	91.7%	2b	4	5	5	4	87.4%
16	12	FBTC	Multifocal	Cryptogenic	11.5	50.0%	2d	4	9	2	2	99.0%
17	23	Myoclonic	IGE	Presumed genetic	13.6	75.0%	3a	4	5	1	1	99.2%
18	23	GTC	IGE	Presumed genetic	14.1	50.0%	3a	4	6	3	3	88.3%
19	14	FBTC	Multifocal	MCD	6.2	50.0%	3a	4	8	3	3	99.0%
20	15	GTC	IGE	Presumed genetic	7.6	33.3%	3a	5	8	5	4	86.3%
21	25	Absence	IGE	Presumed genetic	Explanted after 5 months							

Note: Initial outcomes from Patients 1–4 have been reported previously[12]; this report extends these outcomes to a mean follow-up duration of 1157 days after implantation.

Abbreviations: FBTC, focal to bilateral tonic–clonic; GTC, generalized tonic–clonic; IGE, idiopathic generalized epilepsy; ILAE, International League Against Epilepsy; MCD, malformation of cortical development; MRFU, most recent follow-up; RNS, responsive neurostimulation.

patients with nonlesional FBTC seizures (mean = 93.8%, SD = 7.3%, median = 93.8%) than for other patients (mean = 80.5%, SD = 20.7%, median = 87.1%; $p = .07$, Cohen $d = .7$; Figure 3C). Of the 17 patients with at least 1 year of follow-up, four decreased their number of antiseizure medications, with an overall mean change of 3.0 (SD = 1.1, range = 1–5) to 2.6 (SD = 1.3, range = 0–4) medications (Table 1).

Of the 20 total patients who achieved at least Engel class 3 outcome, the time to worthwhile seizure reduction from time of surgery ranged from 22 days to 840 days after RNS implantation (mean = 254 days, SD = 203 days). Average time to worthwhile seizure reduction (>50% seizure reduction) from time of surgery was significantly faster for patients with myoclonic IGE (mean = 53.7 days, SD = 16.6 days) than for other patients (mean = 289.6 days, SD = 199.6 days; $p < .01$, hazard ratio = 24.8; Figure 3C).

Of the 17 patients with at least 1 year of follow-up, four decreased their number of antiseizure medications, with an overall mean change of 3.0 (SD = 1.1, range = 1–5) to 2.6 (SD = 1.3, range = 0–4) medications (Table 1).

3.2 | Device settings

Twenty patients were programmed over a mean of seven epochs per patient for a total of 140 programming epochs with a mean duration of 156 days. There was no significant difference in the number or duration of epochs between seizure type groups ($p = .81$ and $p = .78$, respectively). The mean time from surgery to enabling stimulation was 60.2 days (SD = 45.5 days). On average, patients underwent 625.6 stimulations per day (SD = 591.7, range = 61.8–2561.7) and had 61.4 long episodes per day (SD = 81.2, range = .4–241.6; Figure 4). Current of stimulation during the latest programming epoch ranged from 1 mA to 7.9 mA (mean = 2.6 mA, SD = 1.8 mA, median = 2.0 mA).

Fifteen patients had at least 52 weeks of poststimulation follow-up (six IGE absence, one IGE generalized tonic–clonic [GTC], two IGE myoclonic, three MCD, and three nonlesional). The mean detector frequency range was higher for MCD (14.2–50.7 Hz) versus all groups (3.2–66.2 Hz; Figures S1 and S2). The mean detector minimum amplitude change was greater for IGE myoclonus (9.4%) and GTC (8.2%) versus all groups (6.4%; Figure S3). MCD was the only group to have a detector frequency sinusoid shape, which was used in 16.6% of weeks ($\chi^2 = 384$, $p < .01$). The mean stimulation charge density was much lower for IGE myoclonus (.84 μC/cm^2) versus all groups (1.31 μC/cm^2). The mean stimulation frequency was higher for both MCD (136.9) and nonlesional (142.9) versus all groups (131.9 Hz).

3.3 | Effect of RNS stimulation on seizure reduction over time

Marginal structural model analysis showed a significant difference for charge density between treatment groups, with greater charge density associated with increased seizure reduction (coefficients with respect to >1.0 μC/cm^2 were ≥1.0 μC/cm^2 and <2.0 μC/cm^2 = .27, ≥2.0 μC/cm^2 and <3.0 μC/cm^2 = .34, and ≥3.0 μC/cm^2 = .37; all $p < .001$; Figure S4). The coefficient for gender was clinically relevant (female = .45), as well as for seizure types IGE-GTC and MCD (coefficients with respect to nonlesions were IGE-GTC = 1.38 and MCD = −.88; all $p < .001$). Cox proportional hazard analysis showed that IGE-GTC and myoclonus had the shortest time to 50% responder rate at 26 and 29 weeks, respectively (Figure S5). The MCD group had the longest time to response, having achieved <25% responder rate at 52 weeks.

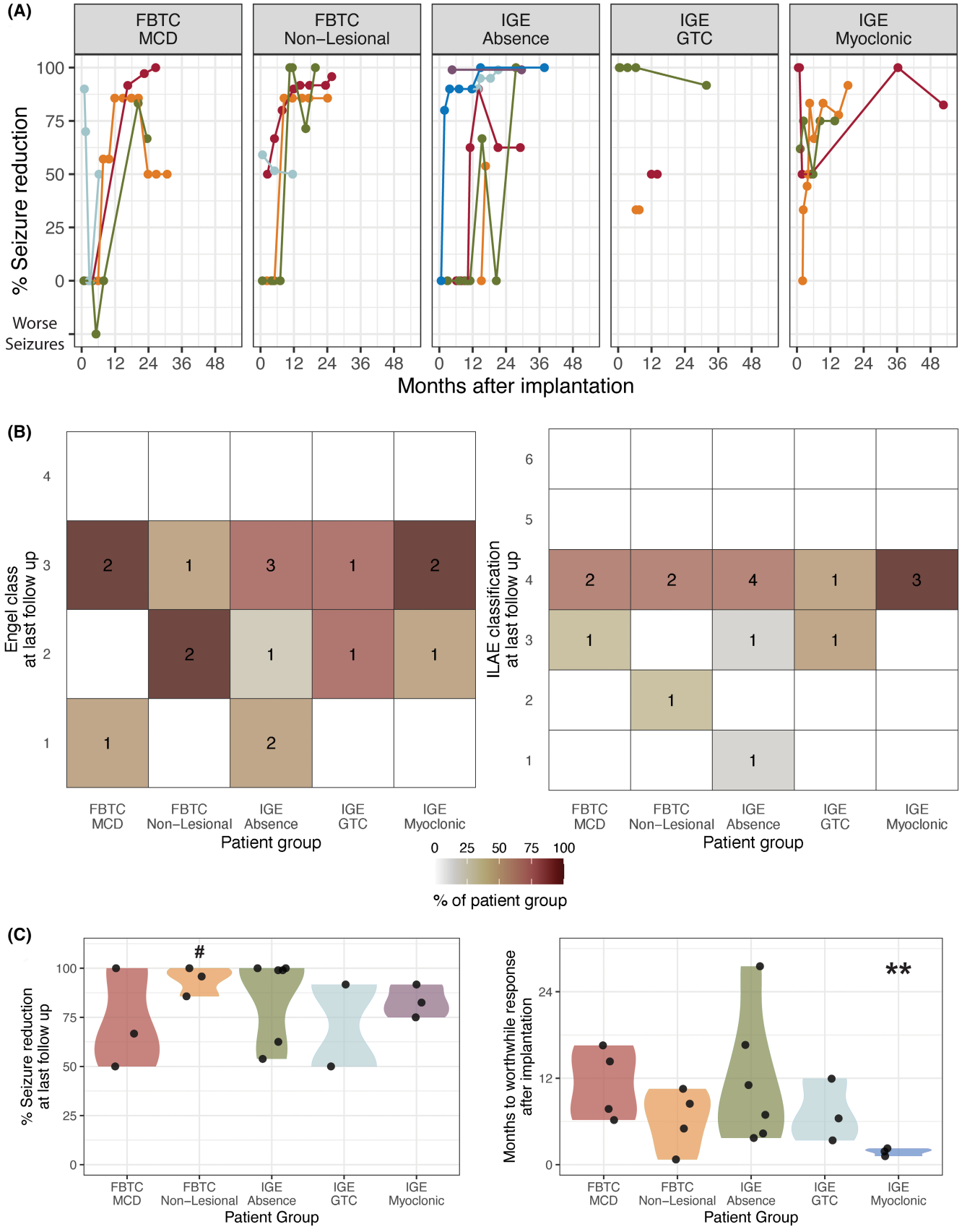
3.3.1 | Long episode detection and patient-reported seizure reduction

Patients downloaded their RNS data from their systems on a mean of 91.6% of days (SD = 13.0%, range = 57.5%–100.0%). For the 16 patients with at least 1 year of downloaded RNS recordings, piecewise regressions yielded a mean average increase of .07 long episodes per day (SD = .19, range = −.14 to .68; Figure 4A). For patients with IGE, there was a significant relationship between percent of seizure frequency reduction at last follow-up and average change in long episodes ($p = .007$, Pearson $r = -.78$; Figure 4B). For patients with multifocal onset FTBC seizures, this relationship was nonsignificant ($p = .33$, Pearson $r = .48$).

3.4 | VTA and surgical targeting

The distal ends of patients' electrodes were on average 7.3 mm lateral, 9.6 mm posterior, and .1 mm inferior to the midcommissural point, the average center of patients' active stimulating contacts per lead was ±8.9, −7.6, +2.6, and the average center of their active sensing pairs of contacts was ±8.6, −7.9, +2.2.

The thalamic nucleus containing the largest percent of VTAs was the ventral posterolateral nucleus (VPL; average = 30.6%, SD = 26.7%), and the nucleus with the second largest percent of VTAs was the CM nucleus



(average = 28.2%, SD = 21.7%; Figure 5A). VTA overlap with the CM nucleus was significantly higher in the 17 patients with direct targeting (average = 33.3%, SD = 20.2%) than in the initial four patients with indirect targeting (average = 8.2%, SD = 13.6%; $p = .02$, Cohen $d = 1.3$; Figure 5A). For patients with at least 1 year of

FIGURE 3 Clinical outcomes stratified by patient groups. (A) Seizure frequency reduction over time after implantation. Connected points indicate percent primary seizure frequency reduction from preoperative baseline for each individual patient. (B) Engel class and International League Against Epilepsy (ILAE) classification at last follow-up for all patients with at least 1 year of clinical follow-up after responsive neurostimulation (RNS) implantation. Color shading refers to the percent of a given patient group with the indicated postsurgical outcome classification. (C) Seizure frequency reduction from preoperative baseline and months after RNS implantation when patients who achieved at least Engel class 3 outcome first reported worthwhile seizure reduction. Points represent individual patient values, and shaded areas depict violin plots illustrating the density of distributions of outcomes per group. Annotations indicate significant or trending differences between groups and the remainder of patients using two-tailed *t*-tests for seizure frequency reduction and Cox proportional hazard analysis for time to worthwhile response (#$p < .1$, **$p < .01$). FBTC, focal to bilateral tonic–clonic; GTC, generalized tonic–clonic; IGE, idiopathic generalized epilepsy; MCD, malformations of cortical development.

follow-up after implantation, VTA overlap with the CM nucleus was not significantly correlated with primary seizure frequency reduction at last follow-up ($p = .22$, $r = -.31$; Figure 5B). The distal contacts for direct targeting (mean AC-PC x = ±6.7, y = −9.0, z = .1) were significantly more medial ($p < .001$, Cohen $d = 2.0$) and more anterior ($p < .001$, Cohen $d = 1.7$) than the distal contacts for indirect targeting (mean MNI x = ±9.8, y = −11.9, z = −1.1; Figure 5C,D).

4 | DISCUSSION

We demonstrated that RNS of the CM region represents an effective, robust, and durable treatment for patients with IGE and multifocal onset FBTC seizures. For the 17 patients with at least 1 year of follow-up after implantation, primary seizure frequency decreased by a mean of 82.6% (median = 91.7%), remaining stable after 1 year of therapy (Figure 3).

4.1 | Seizure reduction across patient groups

Among the patients with multifocal onset FBTC seizures, nonlesional patients exhibited highly favorable outcomes. All three patients with postencephalitic epilepsy experienced >85% reduction in seizure frequency (Figure 3C), and the postencephalitic epilepsy patients experienced a greater average seizure frequency reduction (mean = 93.9%, median = 95.8%) than other patients.

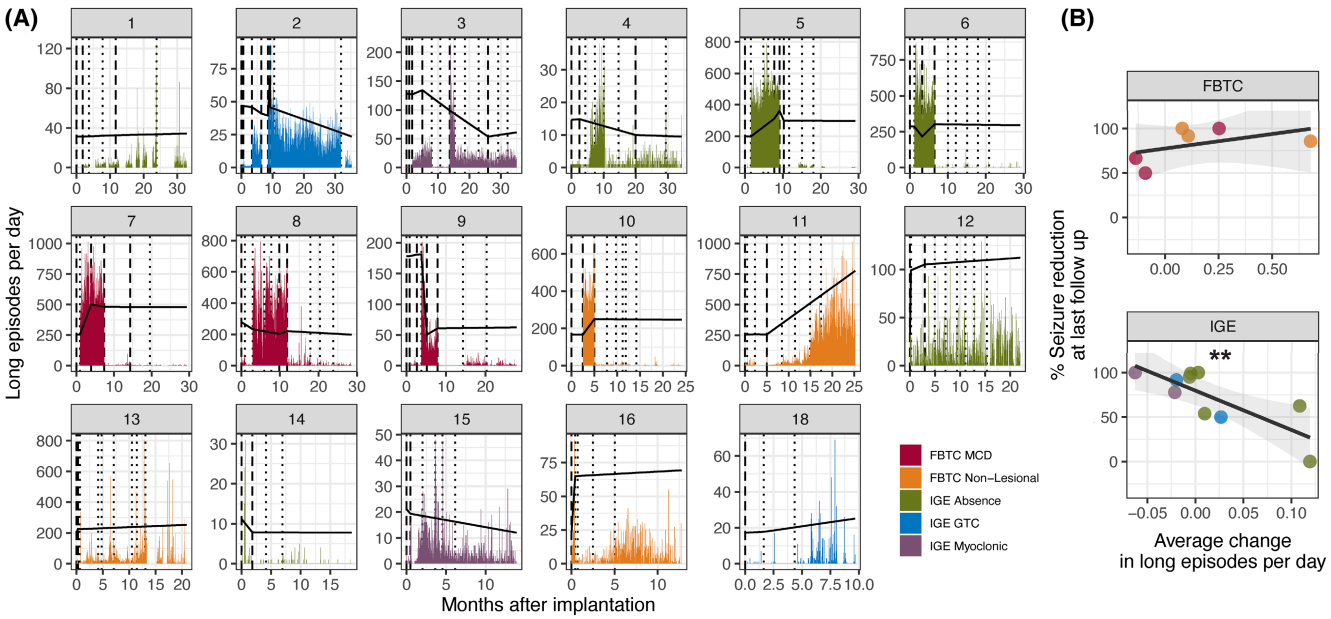


FIGURE 4 Long episodes over time. (A) Long episode events over time after responsive neurostimulation (RNS) implantation for each patient. Dashed vertical lines indicate changes to RNS detection settings, and dotted vertical lines indicate any other RNS programming changes. Trend lines represent piecewise linear regression of long episodes over time, split between epochs of stable detection parameters. (B) Relationship between reported seizure frequency reduction at time point of last available device recordings and average change in long episodes per day, split between patients with multifocal onset focal to bilateral tonic–clonic (FBTC) seizures and idiopathic generalized epilepsy (IGE). Linear trend lines are shown, and shaded areas depict 95% confidence interval. Annotations indicate a significant relationship by Pearson correlation test (**$p < .01$). GTC, generalized tonic–clonic; MCD, malformations of cortical development.

Postencephalitic epilepsy is the most common preventable epilepsy globally[28] and frequently presents with high seizure frequency and drug resistance,[29] and traditional surgery often is not curative, as a large proportion of postencephalitic patients have bilateral or multifocal epilepsy.[30,31] The success of CM RNS in these three patients suggests that it may provide a useful therapy for some challenging cases of this debilitating and otherwise difficult-to-treat disorder.

Patients with lesional multifocal onset FBTC seizures also had excellent outcomes, although somewhat less impressive than their nonlesional counterparts. Among MCD patients with at least 1 year of follow-up, mean seizure frequency reduction was 72.2% (median = 66.7%; Figure 3C). Given the dramatic heterogeneity of these patients' malformations, it is possible that the CM target region was not a uniformly central hub in each patient's seizure network, limiting the effectiveness of CM-region RNS for some. Investigating other thalamic nuclei that may be more relevant to patient-specific seizure networks may be helpful in this category of patients, including for consideration in thalamocortical stimulation strategies or combinatorial strategies that include ablating nodes of the seizure network in combination with RNS.[32]

Interestingly, reductions in seizure frequency often were not accompanied by decreases in antiseizure medications. Only four of 17 patients with at least 1 year of follow-up decreased their number of antiseizure medications, with an overall mean change of 3.0 medications to 2.6 medications (Table 1). Static medical management may be in part due to the reluctance of providers to amend regimens in the perioperative period but also may highlight additional opportunities for quality-of-life improvement in these patients. Given that the RNS system provides objective data for informing antiseizure medication titration,[33] these patients may benefit further from focused attempts to reduce medication concordant with intracranial electroencephalographic review.

Although patients experienced limited medication reductions, and only eight of 17 patients had Engel class 1 or 2 outcomes, the substantial reductions in patients' seizures facilitated meaningful changes in their lives (e.g., reports of no longer requiring a helmet or wheelchair, reports of milder seizures without loss of consciousness, and reports of cognitive clearing among patients with Engel class 3 outcomes). This discrepancy between patients' reported experiences and traditional outcome metrics for epilepsy surgery underscores the need for the development and implementation of outcome scales specific to neuromodulation for epilepsy.

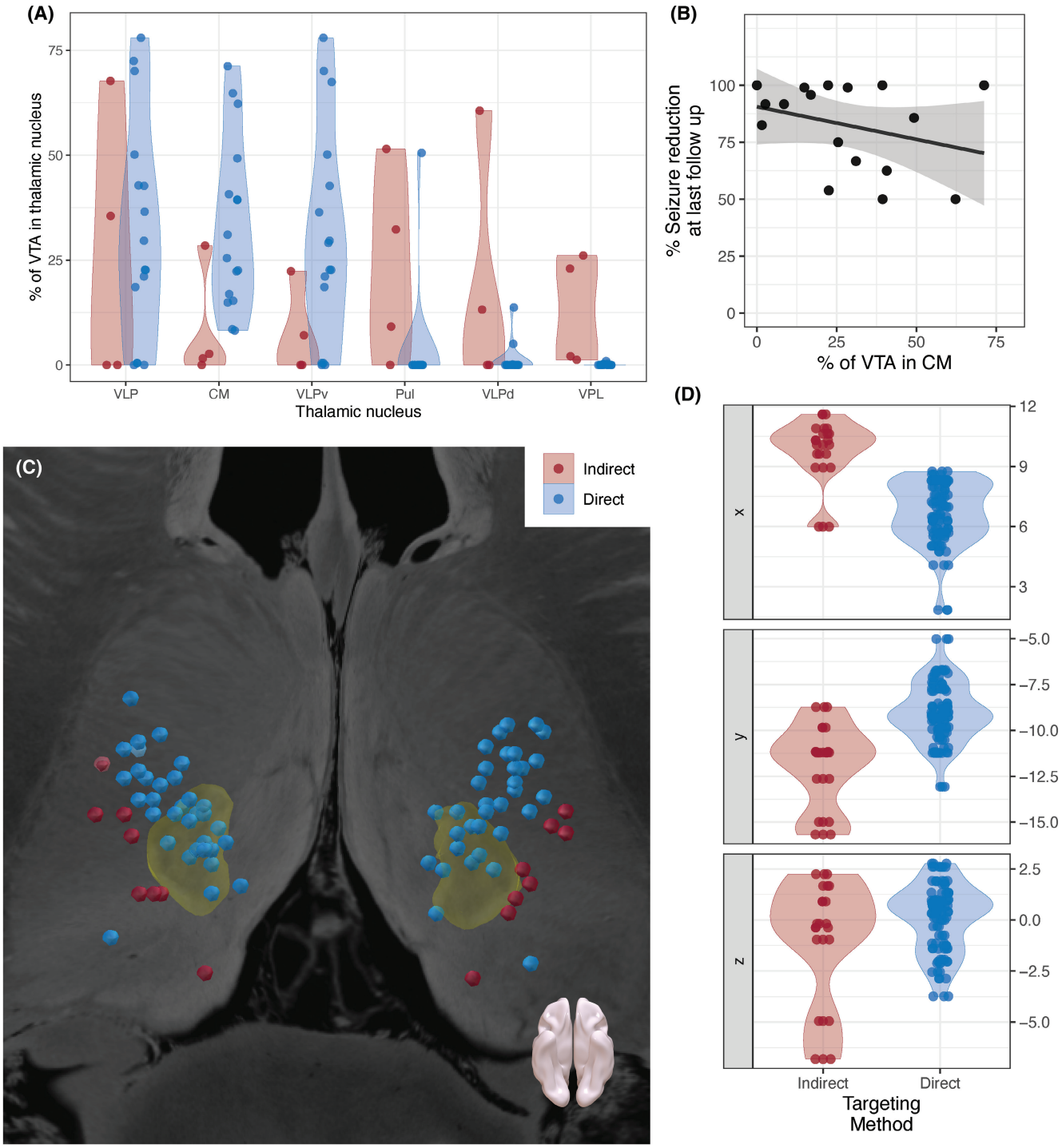
4.2 | Time to response across patient groups

Although all 17 patients with at least 1 year of follow-up experienced a worthwhile reduction in seizures (Figure 3C), the mean time to achieving Engel class 3a outcome after RNS implantation was >8 months.

Within the IGE group, patients with primarily myoclonic seizures demonstrated consistently quicker treatment response than other patients, as all myoclonic IGE patients achieved worthwhile seizure reduction in <3 months (mean = 1.8 months; Figure 3B). Conversely, the IGE patients with primarily absence seizures demonstrated relatively variable response rates, with four patients achieving at least 99% seizure frequency reduction but the other two patients experiencing 50%–65% reduction, with time to worthwhile response ranging from 3 months to 28 months (Figure 3C).

The MCD group had a significantly slower time to response than all other groups. This may be in part due to the heterogeneous nature of malformations and associated dysplasia. Neither imaging nor intracranial EEG may depict the seizure network sufficiently, which in some cases may be less connected to the CM region of

FIGURE 5 Relationship of patient contacts and volumes of tissue activation (VTAs) with thalamic nuclei and association with seizure frequency reduction. (A) Points indicate the percent of patient VTAs overlapping the top six intersected thalamic nuclei defined by the Thalamus Optimized Multi Atlas Segmentation (THOMAS) atlas, split between patients who underwent indirect targeting in red and patients who underwent direct targeting in blue. Shaded areas depict violin plots illustrating the density of the distribution of VTA overlap with thalamic nuclei. (B) Points indicate the relationship between percent of patients' VTAs overlapping the THOMAS atlas definition of the centromedian region (CM) and the percent of primary seizure frequency reduction for patients with at least 1 year of follow-up. Linear trend line is depicted, and shaded area indicates 95% confidence interval. (C) Spheres (1 mm in diameter) represent the centers of contact pairs of patients' implanted electrodes in MNI152 ICBM 2009b NLIN asymmetric space, shown in axial view. Red spheres indicate indirectly targeted electrodes, blue spheres indicate directly targeted electrodes, and the yellow regions represent the THOMAS atlas definition of the CM. Brain orientation is depicted by the schematic at the bottom right of the panel. (D) Points indicate the anterior–posterior commissural x, y, and z coordinates of distal contacts of patients' implanted electrodes (split between patients who underwent indirect targeting in red and patients who underwent direct targeting in blue), with localized electrodes mirrored to the right side. Shaded areas depict violin plots illustrating the density of the distributions of coordinates. Pul, pulvinar; VLP, ventral lateral posterior; VLPd, dorsal part of ventral lateral posterior; VLPv, ventral part of ventral lateral posterior; VPL, ventral posterior lateral.



the thalamus. This notion is supported by this group's atypical detector settings, notable for using a sinusoid frequency shape detector in 16.6% of weeks and having a wider detector frequency range than other groups. Differences in time to response for IGE patients across seizure type further demonstrate the variability of clinical trajectories across patient groups, underscoring the need to stratify analyses by phenotype when estimating treatment effectiveness.

4.3 | Device settings

Greater charge density was correlated with an increase in seizure reduction controlling for primary seizure type. Charge density is an estimate of the stimulation delivered after adjusting for the number of active electrodes and the power per phase. Critically, this value is different from stimulation current, which is a summation of the

total current applied to each electrode or electrode pair in the montage. This finding suggests that increasing the amount of stimulation earlier in a patient's course may improve seizure reduction and reduce time to response.

4.4 | VTA and surgical targeting

Variation in patient outcomes may also be related to variability in contact locations and stimulated thalamic nuclei. A total of 11 thalamic nuclei, as defined by the THOMAS atlas, were covered across all patients' VTAs, with distinct constellations of nuclei for different patients. Moreover, CM stimulation was variable, comprising 0%–71.2% of the VTA. Note that selection of the stimulation contacts is based on detection of the earliest, most epileptiform-appearing signal detected between the sensing bipolar electrode pair on each side, rather than being dependent on assessment of anatomical localization. The heterogeneity in stimulated nuclei also is due to the evolution in targeting methodology in this cohort, from an indirect to direct approach (Figure 5A). Direct targeting facilitated greater stimulation of the CM region, as 33.3% of VTAs overlapped the CM region for directly targeted patients, whereas only 8.2% of VTAs did so for indirectly targeted patients (Figure 5A). The different targeting methods may also have led to stimulation of different subregions within the CM region (Figure 5C), or different white matter pathways, as there were significant differences in the location of directly and indirectly targeted distal contacts (Figure 5D). On average, the directly targeted distal contacts were 3.1 mm medial and 2.9 mm anterior to the indirectly targeted distal contacts. In the evolution of our targeting procedure, based on lead models from this cohort that on average appeared to favor the anterior half of the CM region, we now use starting indirect coordinates of ±8, −11, and 0 from the midcommissural point. Of note, the VPL was the thalamic nucleus with greatest overlap with patients' VTAs. Some patients did intermittently experience sensory changes (e.g., focal numbness and paresthesias), which were tolerated well during chronic stimulation.

As might be expected given the excellent clinical responses observed in those patients targeted indirectly, selective stimulation of the CM region was not predictive of improved outcomes (Figure 5B). The absence of a significant relationship between CM stimulation and clinical outcome indicates that the therapeutic target is not exclusively the CM region proper. Given the variability of response trajectories between groups in our cohort, the optimal region of modulation may vary between groups, precluding a straightforward correlation between outcome and region of stimulation. Therapeutic effects also may be related to contributions of nearby structures to seizure control. For instance, RNS of the medial pulvinar nucleus can be effective in the management of temporal lobe and posterior quadrant neocortical epilepsies.[34,35] Alternately, prior work in IGE and Lennox–Gastaut patients has suggested that neuromodulation of the CM region is optimized in certain parts of the nucleus with particular connectivity patterns, indicating that the CM region cannot be treated monolithically when targeting and evaluating stimulation.[10,36] It is possible also that therapeutic effects are generated primarily by stimulating fibers of passage coursing through this region of the thalamus, akin to the evolution in DBS for essential tremor, where the dentatorubrothalamic tract now is recognized as the target substrate, rather than the ventral intermediate nucleus itself.[37,38]

4.5 | Long episodes and patient-reported seizure reduction

Long episodes have traditionally been used as a method for tracking treatment response. We found a significant correlation between decrease in long episodes and reported percent seizure reduction in patients with IGE (Figure 4B) but not in patients with multifocal onset FBTC seizures (Figure 4B). This discrepancy may suggest that the mechanism of therapeutic action of CM RNS in multifocal onset FBTC seizures may not involve the modulation of primary seizure organization but could instead be related to interference with rapid and broad ictal propagation patterns through the thalamus. Lack of sufficiently sensitive or specific detection settings in this patient population, already characterized by excellent response rates, may also explain the lack of correlation between long episodes and clinical seizure frequency reduction.

4.6 | Future directions

These findings are limited by the retrospective nature of the clinical case reviews, which constrains the level of resolution available for patients' outcomes. Also, although this work represents the largest reported series of CM RNS to date, it is still limited by a relatively low sample size, which may restrict the generalizability of the results and precludes more in-depth stratified analyses.

Future work will address these issues of increased sample sizes and detailed subgroup analyses, especially given the wealth of data being collected in ongoing multicenter trials of bilateral CM RNS for IGE (NCT05147571)

and bilateral thalamic–cortical RNS for Lennox–Gastaut syndrome (NCT05339126). Future grouped connectomic analyses, as have been implemented with other neuropsychiatric disorders[39–41] and certain epilepsy subgroups,[10,36] may provide clarity about optimal targeting. Analyses of patients' own data, potentially including scalp EEG, SEEG, and structural and functional connectivity (as has been applied, for instance, to temporal lobectomy patients[42–44]), may also enable optimization of targeting and RNS system parameter tuning in a more precise patient-specific manner.

5 | CONCLUSIONS

These results indicate the significant promise of bilateral CM-region RNS therapy in patients with drug-resistant IGE and multifocal onset FBTC seizures, who otherwise have few therapeutic options. Ongoing work regarding the refinement of precise stimulation targets, tuning of RNS system parameters, and thoughtful patient selection will continue to improve effectiveness and quality of life.

AUTHOR CONTRIBUTIONS

Conceptualization: Pranav Nanda, Nathaniel Sisterson, and Robert Mark Richardson. Data curation: Pranav Nanda, Nathaniel Sisterson, Ashley Walton, Catherine J. Chu, Sydney S. Cash, Lidia M. V. R. Moura, Joel M. Oster, Alexandra Urban, and Robert Mark Richardson. Formal analysis: Pranav Nanda, Nathaniel Sisterson, and Ashley Walton. Visualization: Pranav Nanda, Nathaniel Sisterson, and Robert Mark Richardson. Writing–original draft: Pranav Nanda, Nathaniel Sisterson, and Robert Mark Richardson. Writing–review & editing: Pranav Nanda, Nathaniel Sisterson, Ashley Walton, Catherine J. Chu, Sydney S. Cash, Lidia M. V. R. Moura, Joel M. Oster, Alexandra Urban, and Robert Mark Richardson.

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CONFLICT OF INTEREST STATEMENT

R.M.R. and A.U. are consultants for NeuroPace. L.M.V.R.M. has served as a consultant for the Epilepsy Foundation and has recently received research funding support from the NIH (NIA 5R01AG073410–02, NIA 1R01AG082693–01, NIH 5U01AG076478–03, NIH 2P01AG032952–13, NIH 5R01AG062282–05), the CDC (U48DP006377–04-00), and the Epilepsy Foundation (60300-EFA-PCO-000-19-01); these disclosures are not relevant to this publication. No other authors have any conflicts of interest to disclose.

DATA AVAILABILITY STATEMENT

Deidentified data are available on reasonable request.

ETHICS STATEMENT

This human subjects research was classified as exempt from the Federal Policy for the Protection of Human Subjects by the Mass General Brigham IRB (Mass General Brigham Protocol No. 2020P000281) due to the minimal risk to subjects of extracting anonymized data from the clinical record.

PATIENT CONSENT STATEMENT

Participants gave informed consent to participate in the study before taking part.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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