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Treatment of drug-resistant epilepsy in patients with periventricular nodular heterotopia using RNS® System: Efficacy and description of chronic electrophysiological recordings

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HIGHLIGHTS

- Periventricular nodular heterotopia (PVNH) can actively participate in epileptogenic networks.
- Low voltage fast activity was the prominent seizure onset pattern in PVNH patients.
- RNS® System therapy reduced clinical seizures by 86% in medically-intractable epilepsy with PVNH.

ABSTRACT

Objectives: Describe changes in clinical seizure frequency and electrophysiological data recorded in patients with medically-intractable seizures and periventricular nodular heterotopias (PVNH) treated with the RNS® System (NeuroPace, Inc., Mountain View, CA).

Methods: Clinical seizures from eight patients (mean follow-up of 10.1 years) were analyzed pre- and post-treatment. Chronic ambulatory electrocorticograms (ECoGs) recorded from PVNHs, hippocampus and neocortex were evaluated to identify the earliest electrographic seizure onset type, pattern of spread, and interictal characteristics.

Results: Mean reduction in disabling seizures was 85.7 % (n = 8); seven patients had >50% seizure reduction and two were seizure-free in the final year of analysis. Seizure rate showed a progressive reduction over the course of the study with the highest rate of improvement in the first two to three years after implantation. Four of seven patients with one PVNH lead and a second lead in the hippocampus or neocortex had some electrographic seizures first recorded at either lead location, suggesting two foci or seizure propagation patterns. Low voltage fast type activity was the prominent seizure onset pattern. Interictal ECoG power was lower in PVNH than hippocampus.

Conclusions: RNS® System treatment substantially reduced clinical seizure frequency in patients with PVNH. Analysis of ictal ECoG records suggests PVNH may be involved in seizure generation.

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Significance: Chronic ECoG recordings suggest PVNH tissue can actively participate in epileptogenic networks. Direct brain-responsive neurostimulation is a safe and effective treatment option in such patients, progressively reducing seizure rate over a period of years.

1. Introduction

Periventricular nodular heterotopia (PVNH) is a type of neuronal migration disorder in which heterotopic groups of neurons are located in the subependymal region. PVNHs may be focal, hemispheric, or bilateral, most often affecting the peri-trigonal region (Battaglia et al., 1997). PVNHs may coexist with other migrational disorders or developmental abnormalities including nodular heterotopias within the white matter and dysplasia of the overlying cortex, suggesting they may share a common cause (Meroni et al., 2009; Tassi et al., 2005). Diffuse PVNHs may be caused by genetic mutations, while focal PVNHs may be due to ischemic injury early in development (Battaglia et al., 1997; Guerrini and Filippi, 2005). PVNHs within the temporal lobes have been associated with mesial temporal sclerosis (Raymond et al., 1994).

PVNHs most often present with medically-intractable epilepsy (Battaglia et al., 1997; Dubeau et al., 1995). However, the specific role of PVNHs in generating seizures and the optimal treatment of such epilepsy has been debated. Several factors obfuscate the role of PVNHs in epileptic circuits, including the high degree of heterogeneity in their distribution, associated structural abnormalities, the sampling error inherent in intracranial EEG, the limited time periods over which intracranial EEG is obtained, and the small number of subjects reported in most studies.

PVNH nodules are clumps of projecting pyramidal neurons, inhibitory interneurons and glial cells in an irregular, non-laminar organization (Meroni et al., 2009). Some PVNHs appear to have reciprocal connections with overlying neocortex as evidenced by photic driving responses with occipital PVNHs or synchronous spikes in the PNVH and overlying cortex (Aghakhani et al., 2005; Tassi et al., 2005). PVNHs appear able to generate interictal discharges but seizures involving PVNHs most often start in synchrony with the overlying cortex (Thompson et al., 2016) and the calculated Epileptogenicity Index (EI) is often higher in associated cortex than in the PVNH (Pizzo et al., 2017). A few case reports have documented PVNHs that generate independent seizures and whose resection is curative (Scherer et al., 2005).

Surgical interventions for medically-intractable epilepsy involving PVNHs have yielded mixed results. PVNHs are often multifocal, deep, and form complex epileptic circuits with associated structures, limiting surgical efficacy. In a case series of nine patients with PVNHs and apparent temporal lobe epilepsy based on video EEG monitoring with sphenoidal electrodes as well as intracranial depth electrode studies in six of the nine patients, none were seizure free at 12 months after temporal lobe surgeries (anterior temporal lobectomy in six, selective amygdalohippocampectomy in one, and anterior temporal lobectomy plus resection of heterotopic tissue in two (Li et al., 1997)). These results may be due to the fact that in most patients the heterotopia(s) were not resected. A series using stereoencephalography (SEEG) to localize the seizure onset zone in order to resect the involved PVNH and neocortical areas or mesial temporal structures produced better results, with three of six patients becoming free of disabling seizures (Aghakhani et al., 2005). Another surgical case series showed excellent responses to resective surgery in all seven patients who had unilateral PVNHs but poorer outcomes in three patients with bilateral heterotopias (Tassi et al., 2005). One of the largest such studies included 14 patients with unilateral PVNH or subcortical nodular heterotopias, of whom 71% (10/14) became free of disabling seizures after surgical resection (Meroni et al., 2009). Newer therapeutic modalities, including MRI-guided interstitial laser thermal therapy, provide the option to lesion multiple epileptogenic heterotopias in some cases, sparing patients the risks of open craniotomies, but their utility may be limited when associated structural abnormalities are extensive (Thompson et al., 2016). Radiofrequency ablation has the added benefit of using the same diagnostic electrodes to lesion tissue, but similar to thermal ablation, the outcomes were modest when the heterotopias were associated with other malformations of cortical development (Cossu et al., 2018). A review of 17 cases of PVNH-related epilepsy treated with radiofrequency ablation at one center produced a seizure-free rate of 76% (13/17) at a mean follow-up of 50 month (Mirandola et al., 2017) but other reviews have not demonstrated as much success with this technique (Pizzo et al., 2017).

The RNS® System uses direct brain-responsive neurostimulation to treat focal epilepsy. Eight adult patients with PVNHs participated in prospective RNS® System clinical trials. Leads were chronically implanted to record electrocorticograms (ECoGs), detect epileptiform activity and provide responsive neurostimulation to the seizure foci. In this case series, neurostimulation reduced clinical seizure frequency in patients with PVNHs despite a variety of treatment approaches. In addition, the chronic ambulatory ECoG data obtained over 10 years provided information on the ictal and interictal electrophysiological characteristics of PVNHs.

2. Methods

All patients in this case series were treated with direct brain-responsive neurostimulation in clinical trials that led to U.S. FDA approval of the RNS® System (NeuroPace, Inc., Mountain View, CA) as an adjunctive treatment for adults with medically intractable focal onset seizures arising from one or two seizure foci. Of 256 patients included in the original multi-center randomized controlled trials, eight patients were diagnosed as having PVNH and are described in this study. Details of the trial designs and results can be found in Morrell et al., 2011 (Morrell, 2011) and Bergey et al., 2015 (Bergey et al., 2015). Electrophysiological data obtained by the RNS Neurostimulator were retrospectively analyzed.

Localization of the seizure foci and targeting of leads were performed as per individual treating physicians and local institutional protocols. Lead placement was confirmed according to local epilepsy center protocols (typically post-implant CT) and individual lead contacts were defined as sampling PVNH tissue, hippocampus, or neocortex.

The RNS® System includes a cranially-implanted programmable neurostimulator connected to two four-contact depth or subdural strip leads placed at the seizure foci. Four differential amplifiers receive input, typically from a pair of adjacent electrodes (1–2 or 3–4), resulting in two ECoG channels from each lead. The neurostimulator is programmed to detect specific EEG activity and to provide direct brain-responsive neurostimulation. Up to six minutes of 4-channel ECoG data can be stored in the neurostimulator at any one time. Stored ECoG records are typically 90 seconds in

duration, and the physician determines whether ECoG storage is triggered by detection of prespecified electrographic patterns, neurostimulation, or according to time of day (scheduled ECoG records). ECoG records are wirelessly uploaded from the neurostimulator to a physician-used programmer or home-use remote monitor and then transferred via the internet to a secure data repository. Data files containing 4-channel ECoG data are termed "ECoG records". "ECoG-channel" or "patient-channel" refer to individual channel data within ECoG records and patients, respectively. All saved records were included in this study. None were considered to be so compromised by artifact so as to be excluded. Amplifier saturations occurred during some larger seizures preventing recording for some time but none occurred during the first 10 seconds of the seizures and for that reason did not affect seizure onset analysis. Episodes of amplifier saturation and detection of prolonged epileptiform discharges or seizures would automatically be flagged as such event types and would not be considered scheduled recordings which were used for the feature extraction analysis described below.

The neurostimulator is programmed by the physician to provide up to five electrical stimulation therapies after detection has occurred. Each therapy has one or two bursts of stimulation. Stimulation parameters (stimulation pathway, amplitude, pulse width, frequency and burst duration) are programmed independently for each stimulation burst. Electrical stimulation artifact prevented recording typically for less than 1 second with delivery of each therapy. These occurred during some recordings following detection of epileptiform discharges but occurred infrequently during the scheduled ECoGs used for the feature extraction analysis, affecting a very small percentage of the overall recording time. When they occurred during the first 10 seconds of seizures used for the onset morphology analysis, only records in which the same seizure pattern clearly occurred before and after stimulation were selected for inclusion.

2.1. Seizure onset analysis

Two neurologists with fellowship training in epilepsy and EEG (authors GN and BR) reviewed ECoG recordings of all event types stored in the Neuropace PDMS database over the mean follow-up time of 10.1 years. Each of the two reviewers scanned four subjects (for a total of 8 subjects included in this study) at various time points in follow-up to select approximately 30 records which satisfied electrographic seizure criteria for at least 10 seconds. A mean of 29.4 (range 27–31) electrographic seizure ECoG records from each of the eight patients were included in this analysis. Only records that both reviewers agreed constituted seizures were analyzed. The two reviewers independently identified the channel(s) involved at the onset of the electrographic seizure, the channels to which seizures spread, seizure onset time, and the electrographic pattern at seizure onset in each of the selected ECoG records for all eight patients. As part of the expert review of the electrographic seizure ECoG records, seizure onset morphology was categorized for the channel on which ictal activity was detected earliest or, in cases with synchronous seizure onsets across multiple channels, was most prominent.

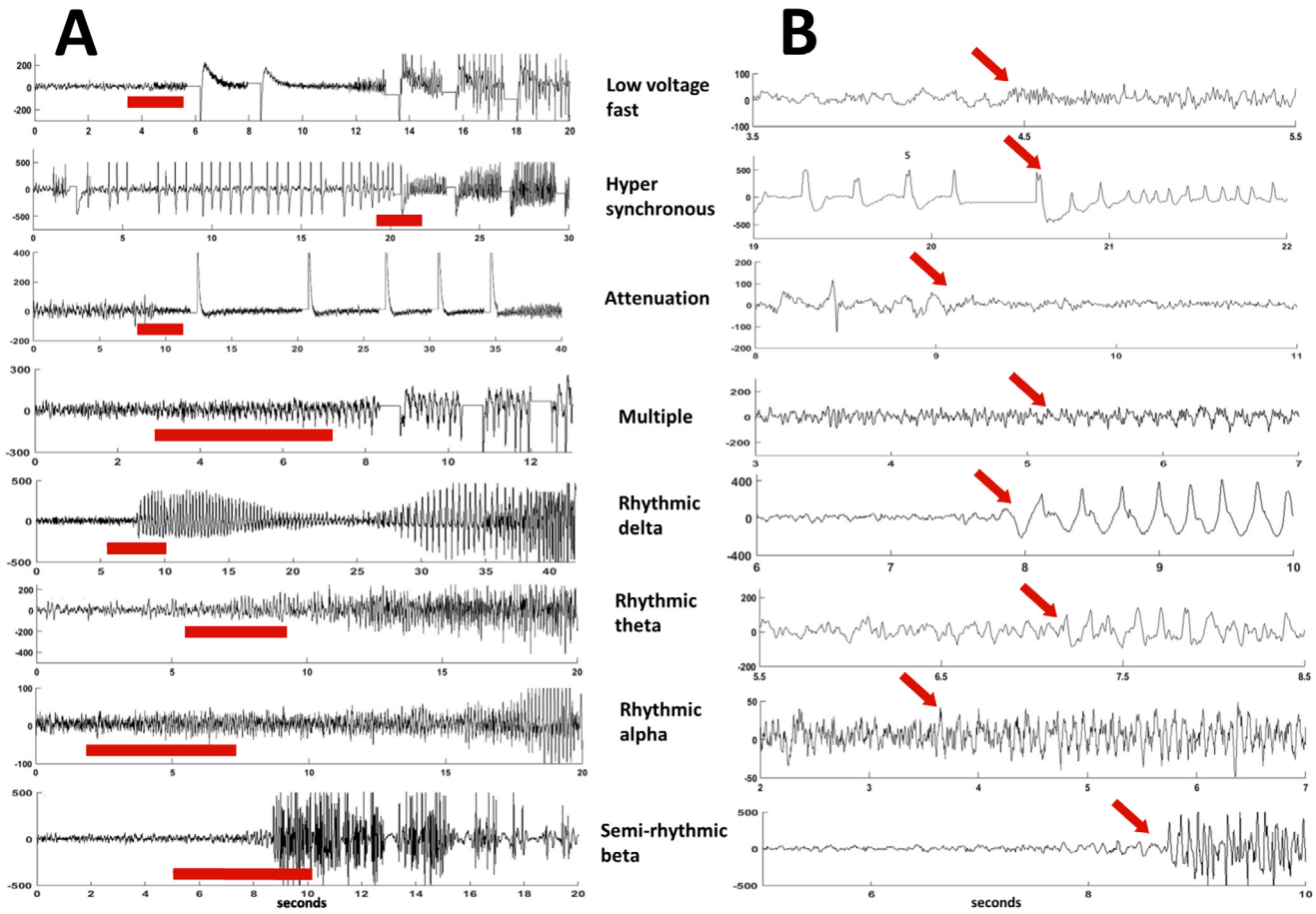


Fig. 1. **(A)** An example of ECoG channel data with the different types of ictal onsets. The activity indicated by the red lines is an example of baseline electrographic activity transitioning into electrographic seizure for each onset type. Responsive stimulation, seen as flat segments followed by amplifier recovery artifact, was delivered during some of these events. Note that example ECoG data were taken from PVNH and non-PVNH patients. **(B)** ECoG channel data with red underlines in Panel A zoomed in to show seizure onset time, indicated with a red arrow.

Electrographic seizures were classified by onset type according to criteria derived from Lee et al., 2000, Spencer et al., 1992, and Perucca et al., 2014. Example electrographic patterns for each of the eight predefined electrographic seizure onset categories are shown in Fig. 1. Definitions of the electrographic seizure onset categories are described in Table S1 of the Supplementary Materials. An electrographic seizure onset pattern had to (a) last at least one second, (b) be a clear change from baseline activity, (c) consist of activity $\geq$3 Hz, and (d) evolve into electrographic seizure activity lasting more than 10 seconds. The seizure onset lead was identified as the lead with the channels containing the earliest ictal onset. In cases of synchronous onsets across multiple contacts, the lead with the highest frequency or amplitude was selected for description. If there was disagreement in any of the reviewed categories, consensus was reached by discussion.

2.2. Feature extraction from scheduled ECoG records

Baseline ECoG records triggered by time of day, called scheduled ECoG records, were used to quantify ECoG features including spike rate (spikes/sec), total spectral power and power in different frequency bands. Scheduled ECoG records are different from electrographic seizure ECoG records whose storage was triggered by prespecified abnormal electrographic patterns. The devices were set to record daily ECoGs but typically storage priority was given to the detection of pre-specified abnormal electrographic patterns (typically electrographic seizures or increase in the prevalence of epileptiform discharges), amplifier saturations, or maget swipes over the device. The rules for prioritizing storage of each recording type varied according to treating physician decision-making. The devices could store four 90-second ECoG recordings and therefore the transfer to PDMS (online database) and availability of records for analysis was also determined by how often the other types of events occurred and by the frequency as well as timing with which subjects interrogated their devices. For example, if the subject interrogated the device soon after the set time of scheduled recording it would be more likely to be transferred for storage in PDMS. However, if the subject interrogated it much later in the day after the set time of the scheduled recording and had multiple other event detections with higher storage priority the scheduled recordings may be overwritten. The number of scheduled ECoG records analyzed from the eight patients was 9530 from the PVNH; 5169 from neocortical channels and 9236 from hippocampal channels. The availability of a large number of scheduled ECoG recordings is reassuring that they are adequately sampling each type of tissue over long periods of time. Methods for extracting features from scheduled ECoG records have been previously published (Sun et al., 2018). Briefly, interictal spikes were defined as peaks in ECoG waveforms with absolute values exceeding 7.5 times the ECoG standard deviation, computed using methods by Quiroga et al., 2004 (Quiroga et al., 2004). Total power and power in different bands were calculated using the Welch method in MATLAB. ECoG features were computed for each channel in scheduled ECoG records from each patient.

To compare scheduled ECoG features between PVNH, neocortical, and hippocampal channels, median values of ECoG features were computed from ECoGs collected per patient and channel (note that each patient can have up to four channels of ECoG data) from every year since implant, and then the mean and standard deviation of these median ECoG features were computed across all patient channels for each type of brain area. Patient years with fewer than four scheduled ECoGs were excluded from analysis. Tests for statistical significance between the three groups were computed using Wilcoxon's rank-sum test on median ECoG features of the PVNH, hippocampal, and neocortical channels with each patient-channel treated independently.

2.3. Clinical outcomes of direct brain-responsive neurostimulation

The clinical results of treatment with the RNS® System were assessed using patient-reported seizure diary information for disabling seizures, defined (using the standard terminology at that time) as simple partial motor (SPM), complex partial (CP), generalized tonic-clonic (GTC), atonic, and tonic seizures. Clinical results were measured as the percent change in total disabling seizures relative to a three-month pre-implant baseline. The percent change in clinical seizure rate was calculated in each three-month epoch prior to a data cutoff of 01-Oct-2017. Clinical results are reported for individual patients and also across the entire group. For all analyses in this paper, a month is defined as 28 days and consequently a year is defined as 336 days. Adverse event data was collected prospectively for the entire length of follow-up according to protocols established for the larger randomized controlled prospective trials.

3. Results

3.1. Demographic and clinical data

Eight of 256 patients in the RNS® System clinical trials had a diagnosis of PVNH. Patient characteristics are provided in Table 1**A**. Patients had high baseline seizure frequencies, had failed to respond adequately to multiple antiepileptic medications, and one each was previously treated with resective surgery or vagus nerve stimulation. Identification of the seizure focus or foci was performed according to the individual epilepsy center's localization protocol. Seizure focus/foci localization was based on imaging and scalp EEG monitoring in four patients and also included intracranial EEG monitoring in the other four patients. Medications remained unchanged during the blinded evaluation period of the randomized control trials but were subsequently allowed to change according to individual treating physician judgement during the long-term follow-up phase of the study.

3.1.1. PVNH location and RNS® System lead implantation strategy

Treatment was aimed at the region(s) suspected to be involved in the seizure focus or foci. A variety of lead placement strategies were employed. Six patients had one lead implanted in PVNH and one lead implanted in the hippocampus or neocortex. One patient had leads implanted symmetrically so that the deepest two contacts sampled hippocampus while the two more proximal contacts targeted peritrigonal PVNH; another patient had both leads implanted in or on the neocortex. Table 1**B** provides details of the lead locations.

3.1.2. Stimulation parameters

Table 2 displays the most recent set of RNS® System stimulation parameters for the eight patients. Stimulation pathway shows cathodal or anodal configurations for each of the four electrodes on the two leads connected to the neurostimulator. Electrodes and leads in the PVNH are highlighted. Epoch length indicates the number of days each patient was programmed with the displayed stimulation parameters. In most cases, stimulation was delivered to both the PVNH and non-PVNH channels.

3.2. Clinical outcomes and adverse events

The mean duration of follow-up was 10.1 years (range 9.3–12.3 years). Fig. 2 describes the clinical seizure frequency outcome results for the eight individual patients (Panel A) and the mean percent change in the clinical seizure rate across the whole group over the entire duration of follow-up (Panel B). The

Table 1
Demographic, clinical characteristics and lead implantation strategy of patients with PVNHs (N = 8).

(A) Demographic and clinical characteristics

Characteristic	Mean ± SD (min–max) or % (n)
Age at enrollment (years)	45.5 ± 10.4 (33–66)
Age of epilepsy onset (years)	19.4 ± 7.5 (15–37)
Duration of epilepsy (years)	15.1 ± 6 (5–20)
Female	50% (4)
Seizure frequency during pre-implant period (seizures/month) ± SD (range)	18.1 ± 23.1 (3–67)
Number of current antiepileptic medications ± SD (range)	2.3 ± 0.9 (1–4)
Prior cortical resection	12.5% (1)
Prior vagus nerve stimulation	12.5% (1)
Prior EEG monitoring with intracranial electrodes	50% (4)

(B) Electroclinical data and lead implantation strategy

Patient	Age (years)	Predominant clinical seizure types	PVNH location and other MRI abnormalities	Seizure onset location[†]	Seizure onset confirmed with Phase II	Lead 1 type and location	Lead 2 type and location
1	49	SPM (8.9%) CP (91.1%) GTC (0.0%)	Bilateral extensive; Left temporal closed-lip schizencephaly	Left occipito-temporal	Yes (PVNH not sampled)	Left PVNH depth	Left posterior temporal neocortex strip
2	35	SPM (0.3%) CPS (99.5%) GTC (0.2%)	Bilateral temporo-occipital	Bilateral temporo-occipital	Yes	Left temporo-occipital PVNH depth	Right temporo-occipital neocortex strip
3	48	SPM (0.0%) CP (100%) GTC (0.0%)	Bilateral most prominent in trigonal areas; Left mesial temporal dysplasia	Left parietal	Yes	Left hippocampus depth	Left parietal PVNH depth
4	33	SPM (0.0%) CP (88.1%) GTC (11.9%)	Bilateral; Other developmental abnormalities	Left (non-mesial) temporal	No	Left temporo-occipital PVNH depth	Left hippocampus depth
5	39	SPM (0.0%) CP (99.9%) GTC (0.1%)	Bilateral temporo-occipital	Right occipital; Right (non-mesial) temporal	No	Right hippocampus depth	Right temporo-occipital PVNH depth
6	45	SPM (0.0%) CP (98.5%) GTC (1.5%)	Right temporo-occipital	Right (non-mesial) temporal; Right occipital	No	Right hippocampus depth	Right occipital PVNH depth
7	49	SPM (82.7%) CP (15.9%) GTC (1.4%)	Bilateral temporo-occipital	Bilateral (mesial) temporal	No	Left posterior hippocampus depth; Occipital horn PVNH depth	Right posterior hippocampus depth; Occipital horn PVNH depth
8	66	SPM (0.0%) CP (97.3%) GTC (2.7%)	Left temporo-occipital	Left frontal; Left lateral temporal	Yes	Left lateral temporal neocortex strip	Left orbitofrontal neocortex strip

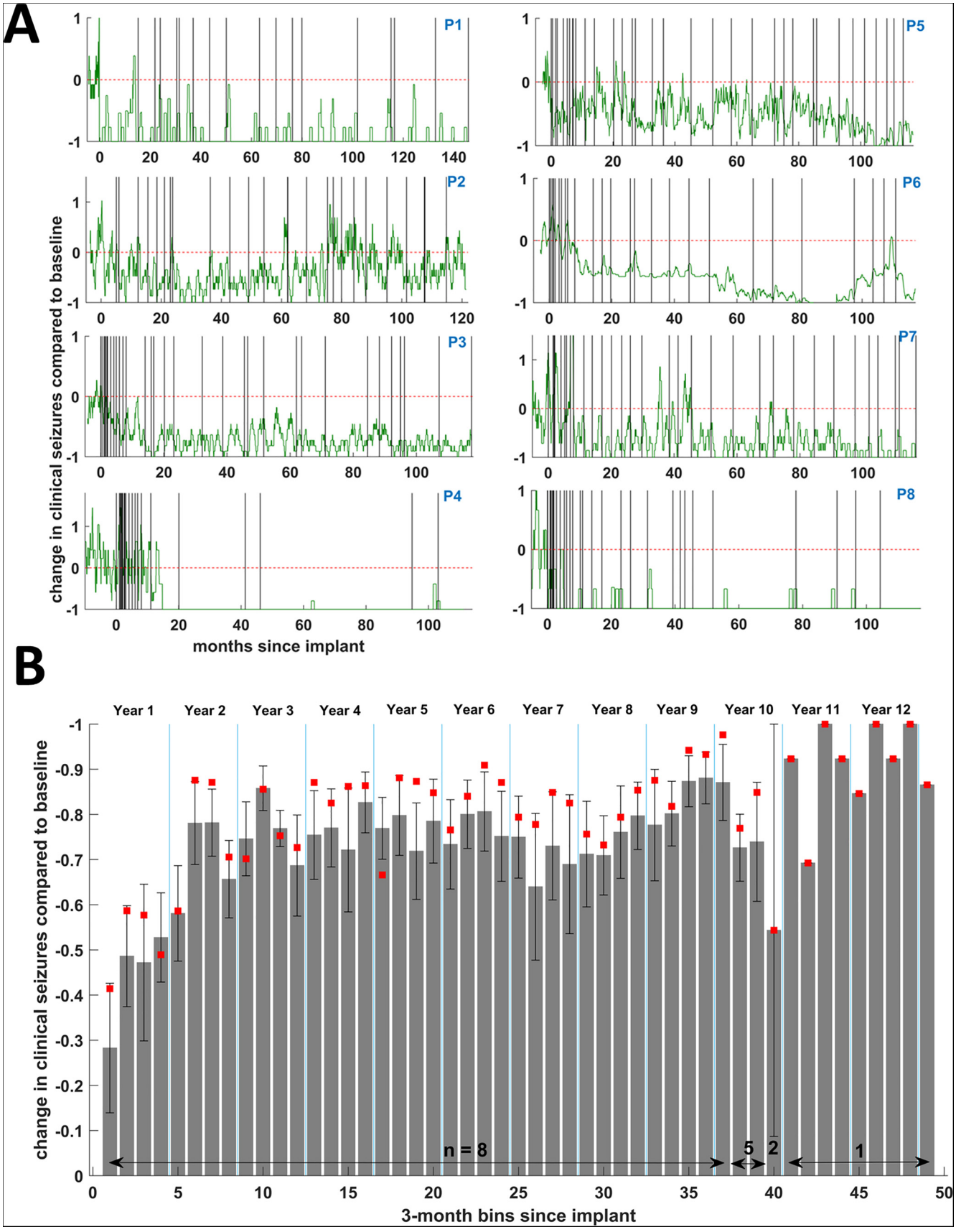
SPM = simple partial motor seizure; CP = complex partial seizure; GTC = secondarily generalized tonic-clonic seizure.
[†] Based on localization testing prior to treatment with the RNS® System.

Table 2
Summary of most recent stimulation settings for each patient (first stimulation to be delivered). Leads and electrodes delivering therapy to PVNHs are highlighted.

Patient	[†] Burst	[*]Stimulation Pathway (lead1) (lead2) (can)	Charge Density (μc/cm^2/phase)	Current (mA)	Pulse Width (μS)	Freq-uency (Hz)	Burst Dura-tion (ms)	Epoch Length (days)
1	1	**(++00)**(0000)(−)	6.1	6.0	160	200	100	3201
	2	**(00++)**(0000)(−)	6.1	6.0	160	200	100	
2	1	**(++00)**(−−−−)(0)	4.4	3.5	200	100	100	387
	2	**(+−00)**(0000)(0)	3.0	1.0	240	100	100	
3	1	(−−−0)**(0000)**(+)	4.1	6.0	160	200	100	595
	2	(0000)**(+−00)**(0)	4.1	2.0	160	200	100	
4	1	**(0000)**(+−+−)(0)	2.5	2.5	160	200	100	2847
	2	**(0000)**(+−+−)(0)	2.5	2.5	160	200	100	
5	1	(−−−−)**(++++)**(0)	1.6	6.5	80	200	150	99
	2	(++++)**(−−−−)**(0)	1.6	6.5	80	200	150	
6	1	(++++)**(−−−−)**(0)	0.6	1.0	200	125	100	183
	2	(+−+−)**(+−+−)**(0)	0.6	1.0	200	125	100	
7	1	(−−**00**)(−−**00**)(+)	0	0	0	0	0	149
	2	(++**00**)(++**00**)(−)	1.5	3.0	160	333	120	
8	1	(++++)(00++)(−)	1.0	3.0	160	100	100	2036
	2	(0000)(00++)(−)	1.0	1.0	160	100	100	

[†] Burst: Each electrical stimulation therapy delivered by the neurostimulator contains two bursts. The physician can program the neurostimulator to deliver up to five therapies when detectors are triggered. Shown in this table are the stimulation settings for therapy one.
[*] Stimulation Pathway: += anode, −=cathode, the last parenthesis refers to programming of the neurostimulator case.

mean reduction in seizures in three-month bins ranged from 80.2% to 88.1% (mean 85.7%) over the last 12 months for which clinical data was available for all patients (bins 34–37 in Fig. 2B). Individual patient seizure reductions ranged from 43.5% to 100% compared to baseline in the last 12 month follow-up (bins 34–37 in Fig. 2B). The seizure rate progressively improved over the first two to three years of therapy, with more modest improvement thereafter.


A
P1
P2
P3
P4
P5
P6
P7
P8
change in clinical seizures compared to baseline
months since implant
B
Year 1
Year 2
Year 3
Year 4
Year 5
Year 6
Year 7
Year 8
Year 9
Year 10
Year 11
Year 12
change in clinical seizures compared to baseline
n = 8
5
2
1
3-month bins since implant

There were no serious surgery-related adverse events and no adverse events due to PVNH stimulation. One patient had dural pain with hippocampal stimulation but it resolved with adjustment of the stimulation current.

3.3. Electrophysiological data

3.3.1. Electrographic seizure onset analysis

The characteristics of electrographic seizures in this group seven patients who had at least one lead in a PVNH and one patient in the neocortex or hippocampus were highly heterogeneous. Representative examples of structural imaging, lead locations, and electrographic seizures from two patients are displayed in Fig. 3**A**. Table 3A shows the distribution of expert-scored seizures between the PVNH and non-PVNH leads in patients one through seven. The eight patient had a diagnosis of PVNH but this was not sampled by the RNS device. On average, 81.6% of all electrographic seizures involved both the PVNH and the non-PVNH leads at some point during the ECoG record. However, three patients had some electrographic seizures that were isolated to the PVNH channels.

An analysis to determine which channels (PVNH or non-PVNH) had the earliest detected electrographic seizure activity is displayed in the right half of Table 3A**.** Electrographic seizures that started synchronously in PVNH and non-PVNH channels were observed in six of the seven patients. Three patients had synchronous onsets in at least 30% of electrographic seizures that were scored. Four patients had at least one electrographic seizure starting earliest over each of the two leads, suggesting two independent seizure generators or variable propagation patterns.

In both PVNH and non-PVNH channels, the most common electrographic seizure onset pattern was low voltage fast activity (50%). This was followed, in order of occurrence, by multiple, semi-rhythmic beta, rhythmic theta, rhythmic alpha, rhythmic delta and attenuation. Hypersynchronous onsets were not observed. The percentage of the electrographic seizure onset patterns in PVNH and non-PVNH areas for each patient and averaged across patients are provided in Table 3B**.**

3.3.2. Interictal electrographic data analysis

Spectral power (total spectral power and power in classic frequency bands) computed from scheduled (baseline) ECoG recordings were assessed for PVNH, neocortical, and hippocampal channels during each year post-implant (see Fig. 3**B**). Total power and power within the different frequency bands was consistently and significantly lower ($p < 0.05$) on the PVNH channels compared to hippocampal channels at all time points after implantation. However, neocortical channels demonstrated significantly higher ($p < 0.05$) total power and power only in the alpha through delta frequency bands than PVNH channels in the first 2–4 years of treatment. As treatment continued, it appeared that low frequency power in the neocortical channels waned and a significant difference could no longer be detected. The interictal spike rate was not significantly different between the PVNH, neocortical, or hippocampal channels and did not clearly change over time, except over the first three years in the hippocampal channels where a decreasing trend in interictal spike rate was seen.

In order to verify that adequate ECoG sampling was performed from each patient over long periods of time, we also plotted the number of ECoG records stored over follow-up time (Supplementary Fig. S1). It is apparent that a much higher number of records are stored in the first several months after implantation. This is often due to patients downloading data more frequently during this time period as the neuromodulation treatment is optimized and the fact that with time less seizures are detected. Blue shading indicates scheduled ECoG records while the gray indicates all other ECoG records. This demonstrates that most patient had sufficient sampling for this analysis. As noted in the methods section, patient years with less than 4 ECoG records were not included in the analysis.

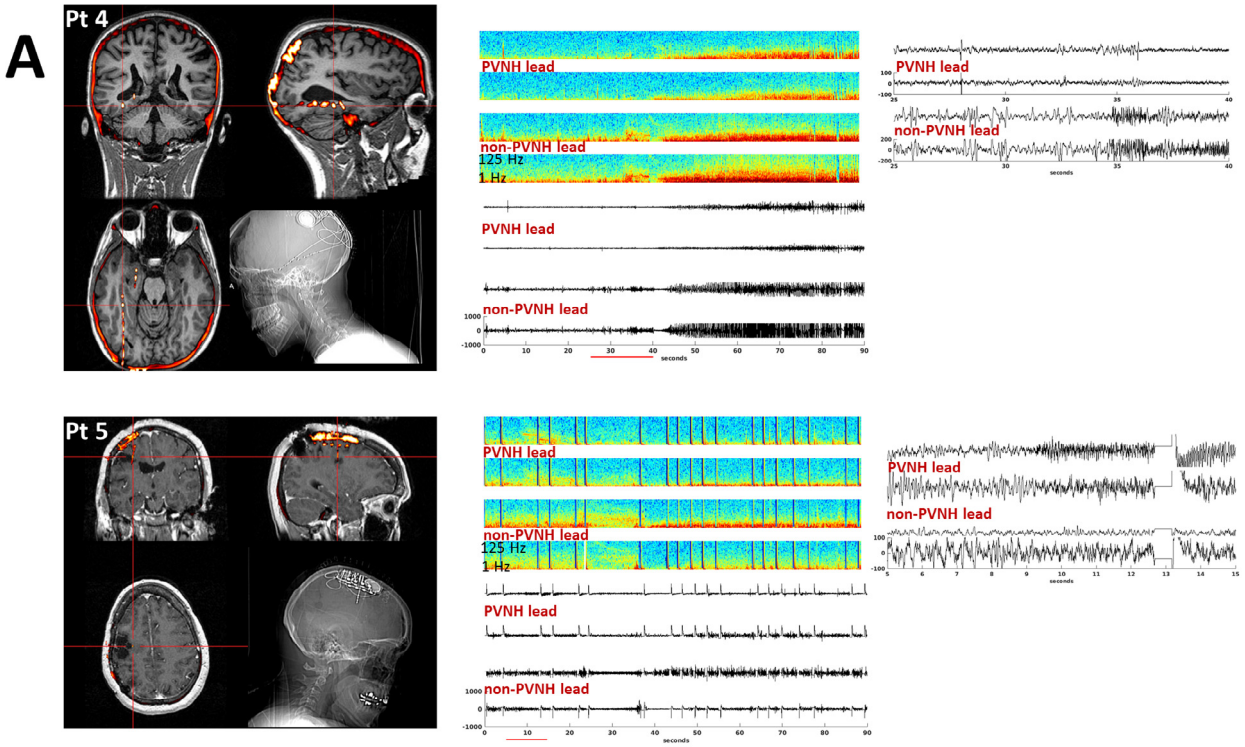
4. Discussion

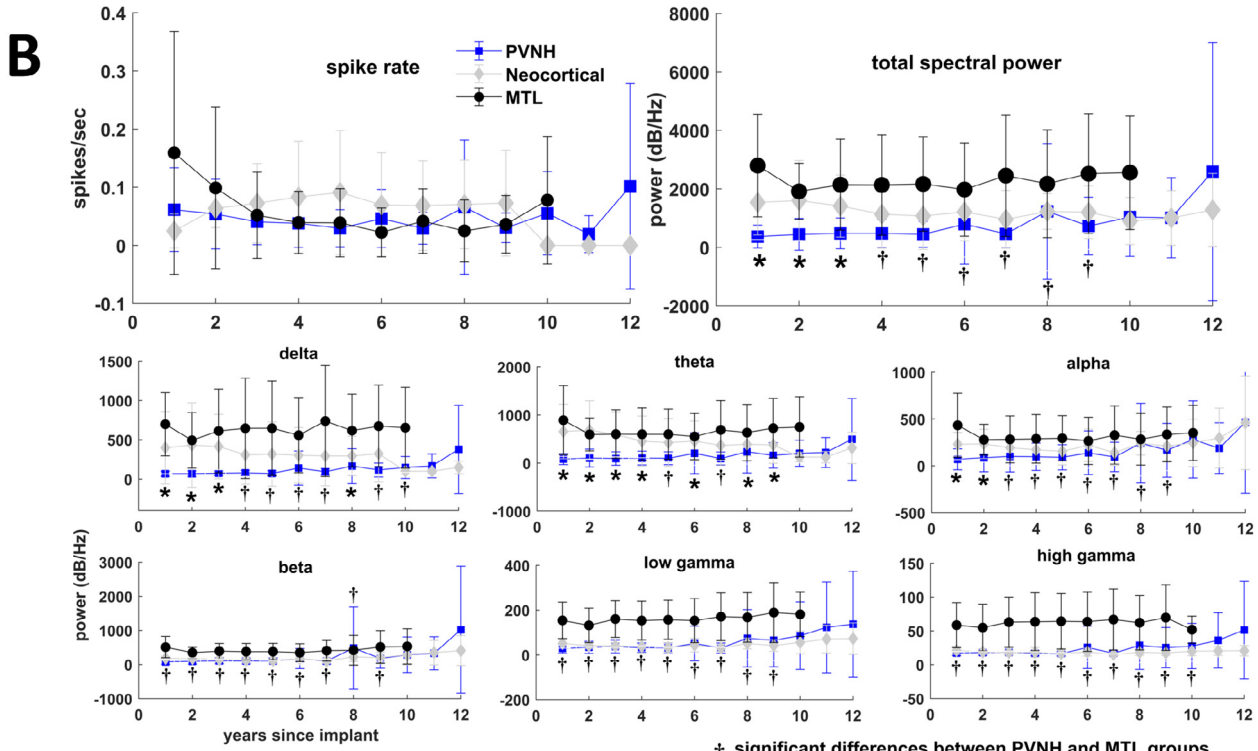
PVNHs most often present clinically with medically-intractable epilepsy. Surgical treatments to resect the heterotopic lesion(s) have yielded mixed results and may be limited because of the risk for functional deficits from resecting eloquent cortex and the often multifocal or diffuse nature of PVNH. Newer treatments, including radio-frequency ablation and MRI-guided laser ablation, allow the lesioning of multiple areas in order to disrupt epileptogenic networks but may be of limited utility when PVNHs are associated with larger epileptogenic structural abnormalities or are closely associated with eloquent cortex. We present a case series of eight patients with severe medically intractable epilepsy due to PVNHs who were treated with direct brain-responsive neurostimulation.

The patients with PVNH treated with neurostimulation experienced a mean clinical seizure reduction of 85.7% and only one patient had a <50% reduction in disabling seizures. These excellent outcomes suggest that patients with PVNH can respond to targeted direct brain-responsive neurostimulation. Favorable clinical responses occurred whether the seizure localization was based on scalp EEG monitoring (four patients) or intracranial EEG monitoring (four patients). This response rate is comparable to the 75% median seizure reduction observed in the larger RNS long-term cohort at nine years follow-up although the small number of patients precludes a clear comparison of response by causes of epilepsy (Nair et al., 2018). The reductions in clinical seizure frequency with neurostimulation continued to improve over time as has been found with clinical trials of other neuromodulation devices (Salanova et al., 2015). In part this could be related to improvements in selection of detection and stimulation parameters as experience with this therapy increased but this phenomenon also suggests that neuromodulation has slow, long-term effects on the underlying epileptic network. Future research will be needed to elucidate the mechanisms by which neuromodulation exerts acute and chronic antiepileptic effects.

One of the perceived advantages of RNS over resective or lesioning procedures is the lower risk of cognitive or neurologic decline. Indeed, this treatment is frequently used in cases of focal eloquent cortex epilepsy. While stimulation parameters are generally set so as not to be subjectively sensed and cognition appears to improve

Fig. 2. (A) Change in clinical seizure rates compared to baseline for each of the 8 PVNH patients (P1 – P8). Red dotted line indicates the baseline seizure rate for each patients and the green plot line shows the mean seizure reduction in 28 day moving average bins (window length was 28 days and window was moved by 1 day for computing moving averages). +1 on the y-axis indicated a 100% increase in clinical seizures and −1 indicates 100% reduction in clinical seizures compared to baseline. Vertical black lines in each plot show timing of device programming changes for each patient. Most patients had higher frequency of programming changes in the first few months after implant with the frequency of programming decreasing as patient's clinical seizure rates improved. **(B)** Mean ± standard deviation change (median change is shown with red dots) in clinical seizure rate in eight patients with PVNH, broken into four three-month bins for each year since implant, compared to a three month baseline period. −1 on the y-axis indicates 100% reduction in clinical seizures with respect to baseline. All 8 patients had clinical seizure rate information available up to thirty-seven (37) 3-month bins after implant.





† significant differences between PVNH and MTL groups
* significant differences between PVNH and MTL groups, and PVNH and neocortical groups

YEAR since implant		1	2	3	4	5	6	7	8	9	10	11	12
N	PVNH	10	9	8	10	10	12	12	10	12	8	4	2
	NEO	4	4	4	6	6	8	6	6	8	4	4	2
	MTL	10	10	8	8	8	8	8	8	8	4	0	0

Table 3A
Distribution of electrographic seizures between PVNH and non-PVNH leads.

Patient	# of electro-graphic seizures sampled	Electrographic Seizures			Earliest Electrographic Seizure Onset		
		PVNH Only	Non- PVNH Only	Both PVNH and Non-PVNH	PVNH	Non-PVNH	Synchronous PVNH and Non-PVNH
1	27	6	0	21	12 (44.4%)	0 (0%)	15 (55.6%)
2	30	5	0	25	29 (96.7%)	0 (0%)	1 (3.3%)
3	30	0	11	19	0 (0%)	21 (70%)	9 (30%)
4	31	0	0	31	3 (9.7%)	22 (71%)	6 (19.4%)
5	28	15	1	12	11 (39.3%)	17 (60.7%)	0 (0%)
6	30	0	0	30	17 (56.7%)	8 (26.7%)	5 (16.7%)
7 †	30	0	0	30	1 (3.3%)	3 (10%)	26 (86.7%)
mean	**29.4**	**3.7**	**1.7**	**24**	**10.4 (35.4%)**	**10.1 (34.4%)**	**8.9 (30.1%)**

† On each lead, two electrodes (one recording channel) were in PVNH and two electrodes were in non-PVNH areas.

Table 3B
Classification of electrographic seizure onsets in PVNH and non-PVNH structures.

Patients	Seizure ECoGs	Channel Location	Most prominent seizure onsets	Low voltage fast	Hypersynchronous	Attenuation	Multiple	Rhythmic delta	Rhythmic theta	Rhythmic alpha	Semi-rhyth-mic beta
1	27	PVNH	27	11 (41%)	0 (0%)	0 (0%)	3 (11%)	1 (4%)	11 (41%)	1 (4%)	0 (0%)
		non-PVNH (Neo)	0	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
2	30	PVNH	30	7 (23%)	0 (0%)	0 (0%)	9 (30%)	1 (3%)	2 (7%)	2 (7%)	9 (30%)
		non-PVNH (Neo)	0	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
3	30	PVNH	0	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
		non-PVNH (Hipp)	30	15 (50%)	0 (0%)	2 (7%)	2 (7%)	0 (0%)	0 (0%)	4 (13%)	7 (23%)
4	31	PVNH	4	0 (0%)	0 (0%)	0 (0%)	1 (25%)	1 (25%)	0 (0%)	1 (25%)	1 (25%)
		non-PVNH (Hipp)	27	6 (22%)	0 (0%)	0 (0%)	14 (52%)	0 (0%)	1 (4%)	3 (11%)	4 (15%)
5	28	PVNH	11	11 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
		non-PVNH (Hipp)	17	1 (6%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (6%)	9 (53%)	6 (35%)
6	30	PVNH	21	17 (81%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (5%)	3 (14%)
		non-PVNH (Hipp)	9	1 (11%)	0 (0%)	0 (0%)	5 (56%)	0 (0%)	0 (0%)	0 (0%)	3 (33%)
7 †	30	PVNH	3	2 (67%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (33%)	0 (0%)	0 (0%)
		non-PVNH (Hipp)	27	25 (93%)	0 (0%)	0 (0%)	1 (4%)	0 (0%)	1 (4%)	0 (0%)	0 (0%)
8 *	29	PVNH	-	-	-	-	-	-	-	-	-
		non-PVNH (Neo)	29	21 (72%)	0 (0%)	0 (0%)	3 (10%)	2 (7%)	1 (3%)	2 (7%)	0 (0%)
Across all patients		PVNH		50%	0%	0%	14%	3%	15%	5%	14%

Rows describing PVNH channels are colored gray, rows with, hippocampal channels are colored green and rows with neocortical channels are colored blue.
†On each lead, two channels were in the PVNH and two channels in non-PVNH areas.
*Both leads were in non-PVNH areas.

Fig. 3. (A) Pre-implant MRI images and RNS® System ECoG records from Patient 4 (top) and Patient 5 (bottom). MRI and scout X-ray from Patient 4 showing a depth lead placed by a temporo-occipital PVNH on the floor of the left lateral ventricle and a second depth lead in the left hippocampal structures. Note that MRIs are displayed as per surgical planning convention with the left brain on the left side of the image. The left images consist of the spectrogram and waveform of a representative 90-second ECoG record showing a seizure beginning in the hippocampal (non-PVNH) channels at approximately 35 seconds and subsequently spreading to the PVNH channels. On the right is the expanded time scale ECoG record demonstrating a semi-rhythmic beta type seizure onset (red underlined portion of left image). MRI images from Patient 5 showing bilateral temporo-occipital PVNHs and scout X-ray showing depth leads in the right hippocampus and the right temporo-occipital PVNH. ECoG records and spectrogram showing a low-voltage fast type seizure onset in the PVNH channels at approximately nine seconds and subsequently spreading to the hippocampal channels. **(B)** Electrographic features from scheduled ECoGs (spike rate, total power, delta power, theta power, alpha power, beta power, low gamma power and high gamma power) on PVNH, hippocampal and neocortical ECoG channels over time. *signifies statistical difference between the two groups PVNH and hippocampal, and PVNH and neocortical channels ($p < 0.05$ using the Wilcoxon rank-sum test). †signifies statistical difference on PVNH and hippocampal ECoG channels. Number of ECoG channels with scheduled ECoGs recorded at each year since implant is shown in the table.

with treatment (Loring et al., 2015), there are surgical risks associated with implantation and generator replacements. At nine years of follow-up, six of 256 patients suffered intra-cranial hemorrhages not due to trauma, with four of these being asymptomatic, and there was a 3.9 % rate of infection per procedure. All but one infections were of soft tissue (Nair et al., 2018). None of the patients described in this study suffered any serious surgery related adverse events.

RNS® System implantation strategy as well as neuromodulation approaches differed across patients. Given the small sample size of this study, further investigation will be required to identify optimal implantation targeting as well as detection and stimulation parameters. Physicians typically designed an initial treatment plan based on the lead location, electrographic seizure activity, and standardized starting stimulation parameters. Five of the seven patients who had leads in both PVNH and non-PVNH structures received stimulation to both. However, in Patient 1, stimulation was only provided to the PVNH, which appeared to be the primary seizure generator, and Patient 7 received stimulation only to the hippocampus. It is generally recommended that the initial detection and stimulation settings be adjusted slowly, systematically, and ideally one at a time in order to optimize the reduction in clinical seizures or detected epileptiform discharges. This iterative approach allows for patient specific optimization of parameters. Stimulation parameter epoch lengths of approximately three to 9.5 years with average of 3.5 years for the last programmed stimulation settings suggest that parameters were changed infrequently towards the end of the treatment period. The most recent parameters used for each patient are displayed in Table 2. Ultimately, a wide variety of stimulation parameters were employed and produced a positive clinical response.

The RNS® System provides chronic ECoG sampling and tracks interictal markers and electrographic seizures over time. It can take several months for ECoG features and electrographic seizures to stabilize after procedures to implant intracranial electrodes (the implant effect) (King-Stephens et al., 2015; Sun et al., 2018). This could impact the reliability of electrophysiological data collected over typically short inpatient video-EEG monitoring evaluations, including assessments with SEEG. Long-term ambulatory ECoG data from the RNS® System provides the opportunity to view each patient's background, interictal and ictal electrophysiology over years.

The results from this study suggest that PVNHs can generate seizures or be involved with the early propagation of seizures. The earliest seizure onsets could be seen in the PVNH channels, the non-PVNH channels (neocortex or hippocampus), or synchronously in the two. Some seizures were isolated to the PVNH channels only. These results are consistent with the findings of SEEG case series (Pizzo et al., 2017; Thompson et al., 2016). Synchronous onsets in PVNH and non-PVNH leads could indicate either a broad epileptogenic network with strong connections between the structures or secondary spread to both structures from a third location. Some patients demonstrated variability in seizure onset locations with some seizures appearing to start in the PVNH channels and others with earliest onset in the non-PVNH channels, arguing for at least two independent seizure foci (assuming stereotyped patterns of seizure progression), or at least two nodes in one epileptogenic network. The conclusion that PVNHs can generate seizures or, at the very least, can be part of the epileptogenic circuit, is further supported by the reduction in seizures in patients receiving brain-responsive stimulation to the PVNH.

Electrographic seizure onset patterns were similar in both PVNH and non-PVNH ECoG channels. The most common type of onset was low voltage fast with gamma or beta frequency activity at onset. This is consistent with a previous case series of five patients with PVNH (Aghakhani et al., 2005). Despite the fact that five of the eight patients in this study (patients 3, 4, 5, 6 and 7) had a lead in the hippocampus and all five had at least some seizures beginning earliest in the hippocampal channels, hypersynchronous patterns were not seen. This suggests a different epileptogenic process than typically seen in mesial temporal lobe epilepsy.

A limitation of the assessment of seizure reduction due to RNS neurostimulation therapy in treating partial seizures in patients with PVNH is that antiseizure medication doses were not controlled after the initial blinded period. However, an analysis of data from the 191 patients in the randomized controlled RNS® System pivotal trial demonstrated that there was not a correlation between the change in clinical seizure frequency and whether the antiseizure medication dosage was increased, decreased or unchanged (Heck et al., 2014).

Other limitations of this analysis include that seizures foci may not have been adequately localized and implanted. The RNS® System records from a maximum of two 4-contact containing leads and seizure focus localization was performed differently among the treating epilepsy centers, raising concern that the leads may not have been optimally placed in the epileptogenic foci to detect the earliest electrographic seizure onset. If this is the case, then the recordings could represent propagated signals or secondary seizure spread. Furthermore, it is possible that not all relevant seizures were detected and stored. However, these patients were treated at experienced comprehensive epilepsy centers that can be presumed to have accurately localized the epileptogenic foci and programmed detection settings appropriately. The large number of analyzed ECoG records is reassuring that the sufficient sampling was obtained.

It should be noted that electrographic seizures do not necessarily represent clinical seizures. An abstract analyzing RNS® System data showed that there is a good correlation between recorded electrographic seizures and clinically reported seizures but electrographic seizures occur much more frequently than clinically reported seizures (Spencer et al., 2018). This is likely due to the fact that if too short or involving only a small area of the brain, such seizures may not produce easily detectable clinical symptoms. It is difficult to judge the extent of clinical symptom based on the electrographic seizure appearance alone. Furthermore, memory is often affected by seizures and patients significantly under-report their clinical seizures in diary data as demonstrated in a study within the setting of the epilepsy monitoring unit (Blum et al., 1996). While not all the recorded electrograhic seizures likely produced easily detectable clinical symptoms, the subjects likely had more clinical events than reported in diaries. Clinicians typically correlate which elecrographic events represent the patient's typical clinical events based on reported seizure diary data or by instructing patient to trigger storage of ECoG recordings by swiping a magnet over the neurostimulator during or immediately after a seizure. Although not all patients are able to use the magnet, these approaches allow the treating physician to optimize seizure detection for the electrographic seizures which also produce clinical events. Approximately 30 electrographic seizures per patient were surveyed so as to judge consistency and accurately sample at least some of a patient's typical clinical events.

In acute SEEG recordings during EMU monitoring, power in a PVNH appears to be lower than in non-PVNH areas (Battaglia et al., 2006; Battaglia et al., 1997). This was also observed in these long-term ambulatory ECoG recordings. Quantitative analyses of scheduled ECoG records containing baseline interictal activity averaged across all patients and ECoG channels showed that spectral power in classic frequency bands was significantly lower in PVNH channels than in channels recording from the hippocampus. The hippocampal channels showed higher power in all frequency bands over the entire length of follow-up. Neocortical channels sampled showed significantly higher power at alpha and lower frequencies

over the first 2–4 years after implant, which appeared to wane over time. Note however that the number of neocortical channels sampled is low, especially in the first few years after implant.

In conclusion, direct brain-responsive neurostimulation was associated with reductions in clinical seizures of more than 85% in patients with medically refractory focal onset seizures and PVNHs. Electrophysiological data suggests that electrographic seizures can arise in the PVNH, from neocortex or hippocampus, or both. Electrographic seizures often showed near simultaneous onsets, suggesting strong interconnectivity between the PVNH and neocortex or hippocampus. Some patient's had some electrographic seizures that started earliest in the PVNH, and other seizures that stared earliest in the neocortical or hippocampal lead, raising the possibility of two independent seizure generators or variable propagation patterns. Most prominent electrographic seizure patterns were similar in the PVNH as in neocortex or hippocampus.

As an alternative to surgical resection, the RNS® System provides a safe and effective therapy that is reversible, modifiable and nondestructive to brain tissue, and provides long-term ambulatory electrophysiological data that may help to better define the seizure focus or network. Based on this small experience, consideration should be given to lead implant strategies that target the PVNH and the neocortical or hippocampal regions that are implicated in the seizure onset or propagation. This will increase the likelihood of an early detection of an electrographic seizure so that stimulation can be provided quickly to the seizure focus/foci, and to the seizure propagation pathway.

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Ethical Publication Statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Disclosure of Conflicts of Interest

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Appendix A. Supplementary material

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