FULL-LENGTH ORIGINAL RESEARCH

Brain-responsive neurostimulation in patients with medically intractable seizures arising from eloquent and other neocortical areas

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Summary

Objective: Evaluate the seizure-reduction response and safety of brain-responsive stimulation in adults with medically intractable partial-onset seizures of neocortical origin.

Methods: Patients with partial seizures of neocortical origin were identified from prospective clinical trials of a brain-responsive neurostimulator (RNS System, NeuroPace). The seizure reduction over years 2–6 postimplantation was calculated by assessing the seizure frequency compared to a preimplantation baseline. Safety was assessed based on reported adverse events. Additional analyses considered safety and seizure reduction according to lobe and functional area (e.g., eloquent cortex) of seizure onset.

Results: There were 126 patients with seizures of neocortical onset. The average follow-up was 6.1 implant years. The median percent seizure reduction was 70% in patients with frontal and parietal seizure onsets, 58% in those with temporal neocortical onsets, and 51% in those with multilobar onsets (last observation carried forward [LOCF] analysis). Twenty-six percent of patients experienced at least one seizure-free period of 6 months or longer and 14% experienced at least one seizure-free period of 1 year or longer. Patients with lesions on magnetic resonance imaging (MRI; 77% reduction, LOCF) and those with normal MRI findings (45% reduction, LOCF) benefitted, although the treatment response was more robust in patients with an MRI lesion ($p = 0.02$, generalized estimating equation [GEE]). There were no differences in the seizure reduction in patients with and without prior epilepsy surgery or vagus nerve stimulation. Stimulation parameters used for treatment did not cause acute or chronic neurologic deficits, even in eloquent cortical areas. The rates of infection (0.017 per patient implant year) and perioperative hemorrhage (0.8%) were not greater than with other neurostimulation devices.

Significance: Brain-responsive stimulation represents a safe and effective treatment option for patients with medically intractable epilepsy, including adults with seizures of neocortical onset, and those with onsets from eloquent cortex.

KEY WORDS: Closed-loop, Neuromodulation, Partial seizures, Eloquent cortex, Brain stimulation.

Key Points

- Responsive stimulation is a well-tolerated treatment option for patients with onsets in neocortical areas, including eloquent cortex
- Median seizure reductions were 58% using a LOCF analysis
- Twenty-six percent of patients experienced at least one seizure-free period ≥6 months and 14% experienced at least one seizure-free period ≥1 year
- Both patients with lesions and those with normal MRIs benefitted, although the treatment response was more robust in patients with a lesion

Seizure outcomes after focal neocortical resection vary depending on whether there is a lesion corresponding to the seizure onset(s).[1] In studies of adults, 53% of patients with a lesion corresponding to the seizure focus were seizure-free after a focal cortical resection, whereas if there was no lesion, only 26% of patients achieved seizure freedom.[2] Whether or not a lesion is identified, patients with seizures arising from eloquent cortex are at risk for neurologic deficits. Depending on the area of brain resected, 17–67% of patients who undergo focal cortical resection of extratemporal areas report new or increased neurologic deficits after surgery.[3–8] Patients who are not good candidates for cortical resection because of risk to neurologic function—such as patients with seizure onsets in eloquent cortex—may consider brain-responsive stimulation as a therapeutic option.

The RNS System (NeuroPace, Mountain View, CA, U.S.A.) is the only brain-responsive neurostimulator approved by the U.S. Food and Drug Administration (FDA) as an adjunctive therapy in reducing the frequency of seizures in individuals with partial-onset seizures who are ≥18 years of age, with ≤2 epileptogenic foci, and who are refractory to ≥2 antiepileptic medications.[9,10] The randomized controlled trial leading to FDA approval demonstrated a significantly greater seizure reduction in patients treated with brain-responsive neurostimulation compared to sham-stimulated patients, with no significant differences in adverse event rates between the two groups.[9] The median percent seizure reduction in the open-arm extension was 44% at 1 year and 53% at 2 years,[11] and ranged from 48% to 66% in years 3–6 in a long-term open-label study.[10] To obtain information about safety and seizure reduction in patients with neocortical seizure foci being treated with brain-responsive stimulation, outcomes were assessed in this subset of patients in the clinical trials of the RNS System, with an additional focus on responses of patients treated in eloquent cortex.

Methods

The RNS System is a closed-loop, brain-responsive neurostimulator. A cranially implanted neurostimulator is connected to depth and/or cortical strip leads that are placed at one or two previously localized seizure foci. Each lead contains four electrode contacts. Two leads can be connected to the neurostimulator at a time, and up to four leads were implanted during the clinical trials. The neurostimulator continually senses electrocorticographic (ECoG) activity through the electrodes. It is programmed by the physician to detect patient-specific ECoG patterns and deliver brief stimulation pulses through the electrodes in response. Physicians adjust detection and stimulation parameters as needed.

Patients in this series had seizures localized to one or two foci in the neocortex. Patients were categorized by lobe of seizure onset based on case report form (CRF) data derived from the presurgical evaluation. Lead placement was determined by CRF or by visual inspection of postoperative imaging. Additional analyses were performed in those subsets of patients with onsets in eloquent cortex and insula. Patients with seizures of frontal onset were included in the

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primary motor group if leads spanned the primary motor cortex and the patient had simple partial motor seizures at baseline. Patients with frontal-onset seizures with leads in Broca's area were identified, as were patients with leads spanning the left superior posterior temporal gyrus (Wernicke's area). Common lead placement strategies are depicted in Figure 1. All patients provided written informed consent. The studies were registered on

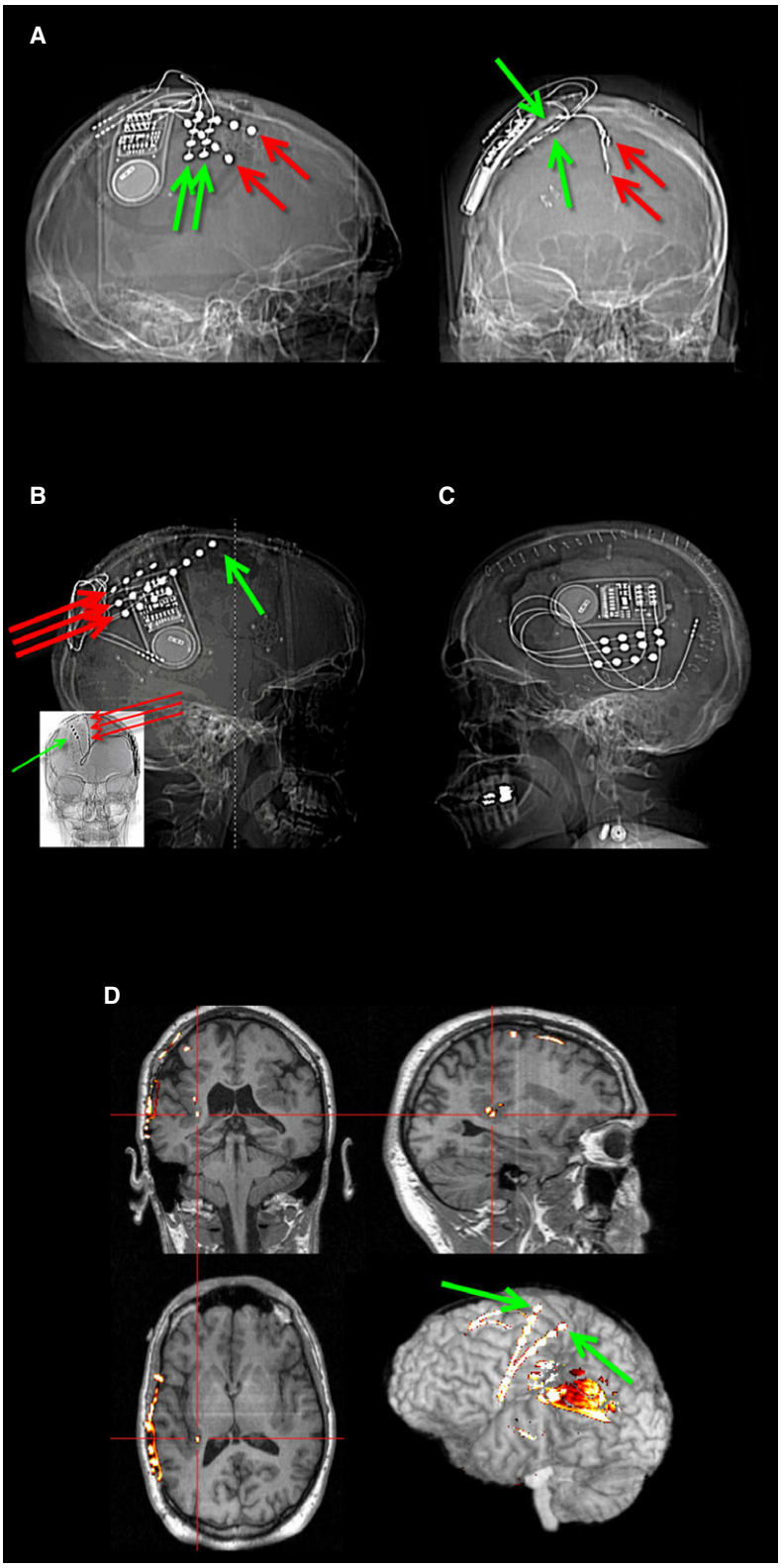

Figure 1.
Lead placement strategies. Patient A had simple partial seizures characterized by left-sided tingling and/or weakness followed by bilateral motor signs. Two leads were placed over the right frontal lobe in the interhemispheric space (red arrows) and two leads spanning the superior aspect of the right lateral frontal lobe (green arrows). The superior interhemispheric lead and the posterior lateral lead were connected to the neurostimulator. Patient B had complex partial seizures characterized by pressure and butterflies in the stomach followed by vocalization and loss of balance. Three leads were placed over the parietal lobe in the interhemispheric space (red arrows), and an additional lead was placed on the right lateral parietal cortex (green arrow). The anterior and posterior superior interhemispheric leads were connected to the neurostimulator. Patient C had generalized tonic–clonic seizures in addition to simple and complex partial seizures characterized by a loss of hearing. Three cortical strip leads were placed over the left posterior temporal lobe. Patient D had simple partial seizures with motor signs on the right as well as complex partial seizures with loss of awareness. Two depth leads were targeted at the anterior and posterior left insular cortex and two cortical strip leads were placed over the left frontal and anterior parietal cortices (green arrows). The posterior insular lead and frontal strip lead were connected to the neurostimulator. © 2017 NeuroPace, Inc.

www.clinicaltrials.gov (NCT00079781, NCT00264810, and NCT00572195).

For subset analyses of seizure reduction by region of onset, only patients who received stimulation in the brain region of interest and had seizure frequency data in the open-label period were included. To control for possible effects of patient withdrawal, last observation carried forward (LOCF) analyses were performed using the most recent 3 months of data (84 days) available for that patient before the data cutoff (November 1, 2014). To examine the response over time, the median percent change in seizures was calculated for each 3-month period during which seizure data were available. Missing days of seizure diary data were not imputed as seizure-free.

Generalized estimating equations (GEEs) were used to determine whether changes in response to treatment varied according to demographic characteristics. GEEs are an extension of generalized linear modeling that handle missing data and properly assign significance to multiple correlated measurements.[12] The percent change in seizure rate for all available 3-month epochs during the open-label period was analyzed using a GEE model with a compound symmetric correlation structure. p-Values are based on empirical standard errors.

Adverse event (AE) and daily patient-reported seizure diary data were collected every 6 months. Adverse events were adjudicated by the physician as device related, of uncertain device relation, or not device related. Serious adverse events were defined as those requiring hospitalization. An independent Data Monitoring Committee reviewed all AEs and a second committee determined whether deaths met criteria for Sudden Unexpected Death in Epilepsy (SUDEP). All study protocols were approved by the institutional review boards of participating investigational sites.

Results

One hundred twenty-six patients in the RNS System trials were identified as having seizures of neocortical origin. This pool of patients included patients from the RNS System Feasibility (n = 45) and Pivotal Trials (n = 81). Patients were followed for an average of 6.1 ± 2.6 patient implant years with an accumulated experience of 774 patient implant years and 719 stimulation years. Patient accountability is shown in S1. Demographic characteristics of these patients are presented in Table 1.

Stimulation was delivered at current amplitudes that varied from 0.5 mA to 12.0 mA. The most common settings were 3.0 mA, followed by 6.0 and 12.0 mA. Stimulation frequency was usually set at 100 or 200 Hz, pulse width at 160 μs, and burst duration at 100 msec. The most common charge density delivered was 6.1 $\mu C/cm^2$. The median number of stimulations delivered per day was 799 (range: 2–3,167), resulting in <10 min of stimulation delivered per day at standard settings. The number of stimulations per day was similar for patients with and without dysplasia.

Table 1. Baseline and demographic characteristics of patients in the RNS system trials with seizure onsets of neocortical origin

Characteristic	Mean ± SD (min-max) or % (n)
Age (years)	30.4 ± 10.1 (18–63)
Female	50% (63)
Duration of epilepsy (years)	19.5 ± 10.2 (4–47)
Number of AEDs at enrollment	3.1 ± 1.1 (1–6)
Baseline seizure frequency (disabling seizures/month)	88.0 ± 246.7 (0[a]–2,320) median = 20.0
Seizure onset	
Frontal	31% (39)
Parietal	13% (17)
Temporal	25% (32)
Occipital	3% (4)
Multilobar	27% (34)
Lesion on imaging	55% (69)
Dysplasia	29% (37)
Other	25% (32)
Number of seizure foci – two (vs. one)	26% (33)
Prior therapeutic surgery for epilepsy[b]	52% (65)
Prior EEG monitoring with intracranial electrodes[c]	82% (103)
Prior VNS	37% (46)

(N = 126).AED, antiepileptic drug; EEG, electroencephalogram; VNS, vagus nerve stimulator.

[a]One patient in the Feasibility Trial had only simple partial sensory seizures during the 3-month baseline.

[b]Resection only (n = 52); subpial transection only (n = 5); callosotomy only (n = 2); Resection + Subpial transection (n = 4); Resection + Callosotomy (n = 2).

[c]17/23 patients who did not have intracranial monitoring had a lesion on neuroimaging.

Seizure reduction

Of the 126 patients with seizures of neocortical onset, 122 had seizure frequency data during the open label-period. Of these, 120 patients had >1 year of follow-up, and 87 had at least 6 years of follow-up. There was a reduction in seizures with treatment with the RNS System that continued to improve with time. The median percent reduction in seizures at the end of year 2 was 44%, and over years 5 and 6 ranged from 61% to 76% (Fig. 2). The improvement was not due to patient withdrawals; an LOCF analysis showed a median percent change of −58% (interquartile range [IQR] −11% to −95%) and a responder rate of 55% (95% confidence interval [CI] 46–63%). Some patients had prolonged periods of seizure freedom. During the open-label period, 37% of patients had at least one seizure-free interval lasting ≥3 months, 26% had at least one lasting ≥6 months, and 14% had at least one lasting ≥1 year.

Seizure reductions were analyzed by demographic characteristic (Table 2). Seizure reductions were not different in

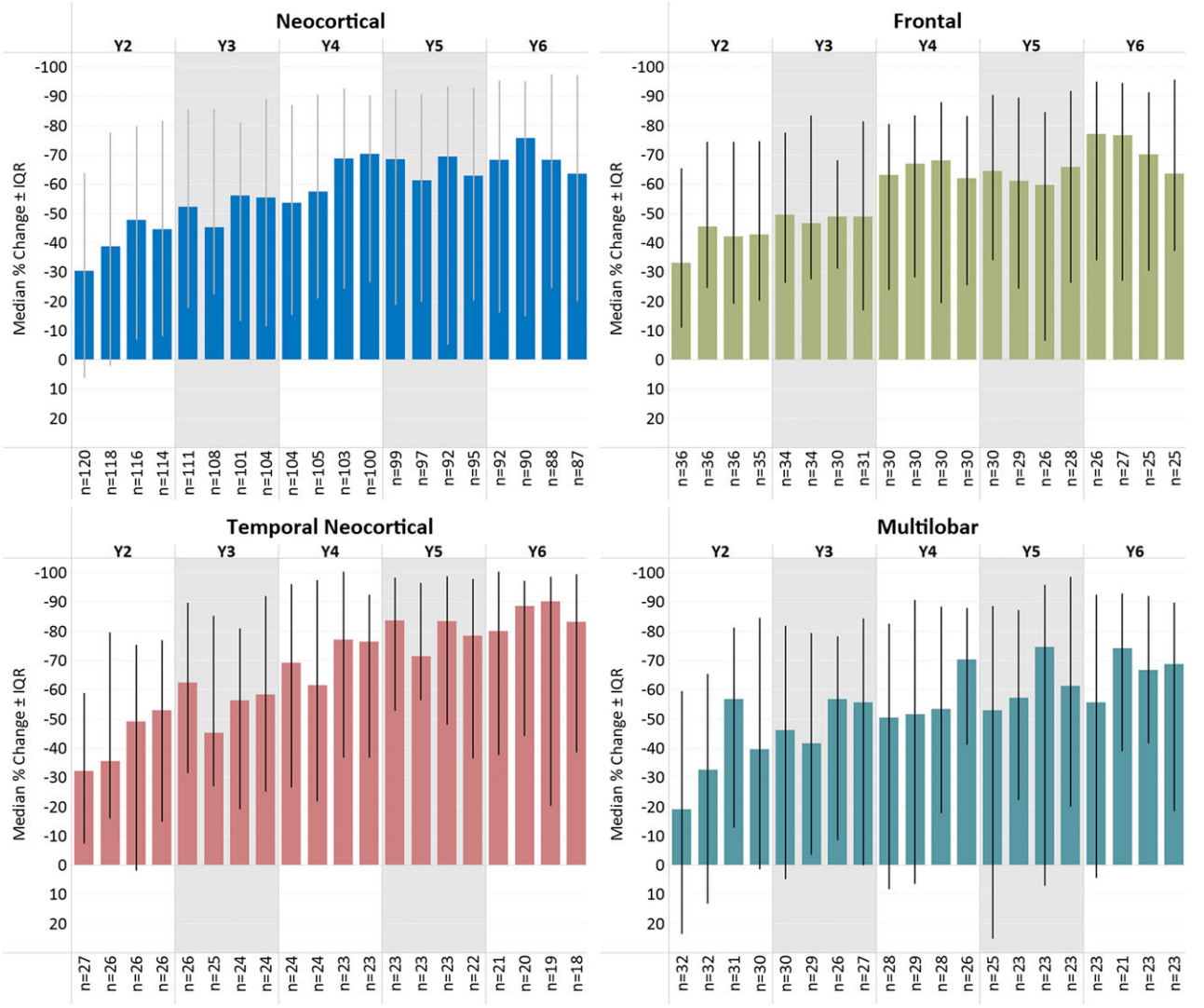

Figure 2.

Median percent change in disabling seizures during the open label period. Observed median percent seizure reduction in 3-month epochs over the duration of follow-up (years 2–6). Blue: All Neocortical; Green: Frontal; Red: Temporal; Teal: Multilobar. The study is ongoing and not all patients have completed all 7 years; therefore, the number of patients decreases over time. Aggregated data are presented for groups with at least 20 patients. Responses for smaller groups (i.e., parietal, occipital, and eloquent cortical areas) are presented in Table 3. IQR, interquartile range, 25th to 75th percentile.

patients who had been treated with a previous epilepsy surgery compared to those who had not ($p = 0.12$), and in those treated previously with vagus nerve stimulation (VNS) and those who had not ($p = 0.20$). There were also no significant differences that could be attributed to having had intracranial monitoring to localize the seizure focus ($p = 0.08$). It should be noted that the majority of patients (82%, 103/126) underwent intracranial monitoring to localize the seizure focus, and most patients who did not do so had a structural lesion (74%, 17/23). Both patients with and without structural lesions experienced a reduction in seizure frequency. The reduction was greater in patients with a structural lesion (77%, LOCF) than in those without one (45%, LOCF), and the difference between these groups was significant over the entire follow-up ($p = 0.02$, GEE).

Safety

There were nine serious adverse events related to intracranial hemorrhage. In six of the nine patients, hemorrhages were attributed to seizure-related head trauma (4.8%). Of the three patients who had non–seizure-related hemorrhages, one patient (0.8%) had a perioperative subdural hematoma that was evacuated with no neurologic consequences. Two patients (1.6%) had cerebral hemorrhages several years after implantation. One was considered device related, and the patient had transient arm and hand weakness

Table 2. Seizure reduction according to demographic characteristics, LOCF analysis.

Characteristic		N	Median % change (IQR)	Responder rate (95% CI)
Prior intracranial monitoring	Yes	99	−58% (−6% to −96%)	54% (44% to 63%)
	No	23	−57% (−32% to −83%)	61% (41% to 78%)
Lesion on neuroimaging	Yes	67	−77% (−27% to −100%)	61% (49% to 72%)
	No	55	−45% (−1% to −82%)	47% (35% to 60%)
Prior therapeutic epilepsy surgery	Yes	62	−54% (−15% to −92%)	53% (41% to 65%)
	No	60	−62% (−10% to −96%)	57% (44% to 68%)
Prior VNS	Yes	44	−50% (8% to −90%)	50% (36% to 64%)
	No	78	−62% (−27% to −99%)	58% (47% to 68%)

LOCF, last observation carried forward; IQR, interquartile range, 25th to 75th percentile; VNS, vagus nerve stimulator.

Table 3. Seizure reduction by lobe of onset and functional area.

	N	[Individual LOCF change in seizures] or LOCF median % change (IQR)	LOCF responder rate (95% CI)
By lobe of onset			
Frontal[a]	37	−70% (−14% to −95%)	54% (38% to 69%)
Parietal	12	−70% (−25% to −93%)	58% (32% to 81%)
Temporal	27	−58% (−38% to −97%)	67% (48% to 81%)
Occipital	4	[−100%, −100%, −38%, −4%]	
Multilobar	33	−51% (7% to −91%)	52% (35% to 67%)
By functional			
Primary motor[b]	17	−83% (−43% to −95%)	65% (41% to 83%)
Broca's[b]	2	[−100%, −91%]	
Wernicke's[c]	5	[−78%, −54%, −45%, −8%, 56%]	
Primary visual[d]	3	[−100%, −38%, −4%]	

LOCF, last observation carried forward (most recent 3 months); IQR, interquartile range, 25th to 75th percentile.

[a]Change in seizures for the 8 patients with frontal onsets and interhemispheric lead placement was [−100%, −95%, −89%, −40%, −23%, −3%, 1%, 65%].

[b]A subset of the 37 patients with seizures of frontal onset. An individual patient can be in more than one subset (e.g., data from a patient with a lead in primary motor cortex and one in Broca's area will be in both groups).

[c]A subset of the 27 patients with seizure onset(s) in non-mesial temporal areas.

[d]A subset of the 4 patients with seizure onset(s) in the occipital lobe.

and ultimately had the neurostimulator and leads explanted. The second cerebral hemorrhage was considered to be of uncertain device relation; the patient was hospitalized with severe headache. An intracranial hemorrhage over the temporal lobe and signs of vasospasm were noted on imaging. The event resolved and the patient continued to be treated with the RNS System.

There were 13 serious AEs related to infection in 13 patients over 774 patient implant years, for a rate of 0.017 infections per patient implant year. One of these infections was attributed to a scalp abrasion sustained during a seizure. Nine of the 13 patients had the neurostimulator explanted and 6 had leads removed as well. Two of these patients were later re-implanted with a neurostimulator. One of the two patients developed an osteomyelitis that was classified by the investigator as of uncertain device relation. This patient had multiple procedures in the week after the explant, including implantation of subdural grids, resection of premotor cortex, and reimplantation of a neurostimulator and cortical strip leads. The infection, which was noted 6 days after the resection, resolved and the wound healed well. There were no instances of treatment emergent meningitis or brain parenchyma infections.

Two patients (1.6%) developed scalp erosions over the neurostimulator. One of these patients had two erosions. The neurostimulator in this patient was placed in a partial thickness craniotomy so that the neurostimulator lay above the skull, rather than the flush profile achieved with a full-thickness craniotomy.

There were five deaths: one by suicide in a patient with a history of depression who was not being treated with responsive stimulation at the time of the event, one due to status epilepticus in a patient whose levels of antiepileptic medications were subtherapeutic, one due to lymphoma, and two that were attributed to definite SUDEP.

The only serious AEs (device-related or of uncertain device relation) that occurred in ≥5.0% of patients were implant-site infection (discussed above) and premature battery depletion, which occurred in eight patients (6.3%). All of these events occurred with a battery made by a manufacturer that is no longer in use. No patient had seizure-related adverse events with initiation of stimulation and no patient withdrew from the study due to a seizure-related adverse event.

Outcomes by lobe of seizure onset

The LOCF percent change and responder rates for patients by lobe of onset and for areas of eloquent cortex are shown in Table 3, and the median percent change in seizures over time by lobe of onset is shown in Figure 2. Brain-responsive stimulation was effective at reducing seizures in all lobes of the neocortex. Examples of the electrographic seizure onsets by lobe of onset recorded by the RNS System are provided in Figure 3. There were no mild or serious device-related AEs such as involuntary motor activity in frontal patients when leads were placed over primary motor cortex. The patients receiving stimulation in either Broca's area or Wernicke's area did not have any device-

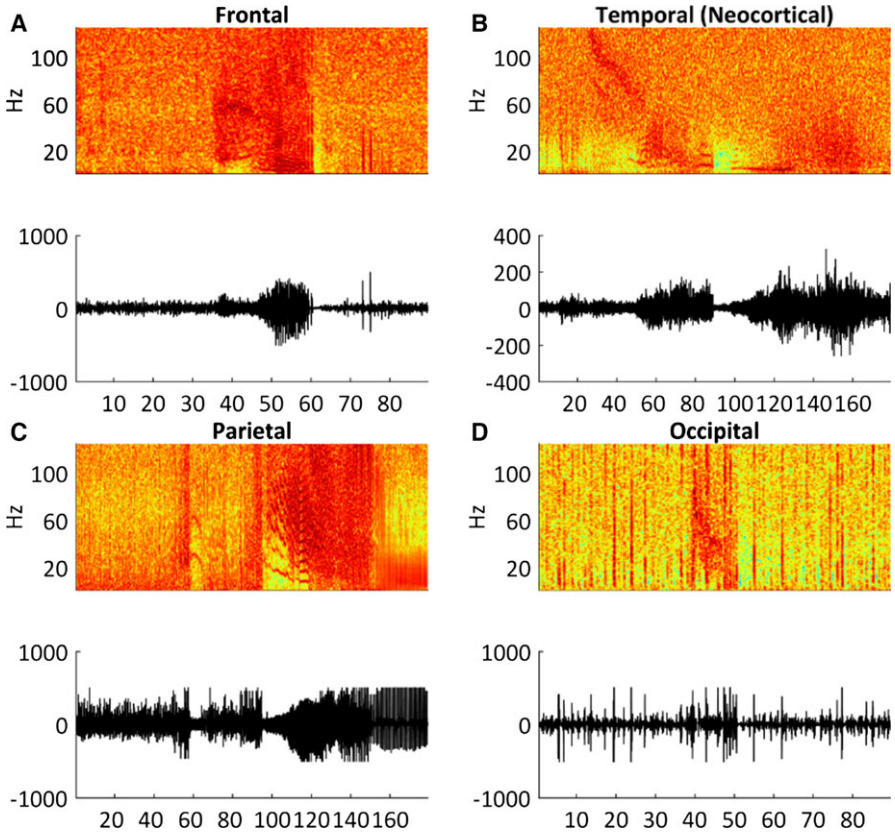

Figure 3.
Examples of seizure by lobe of onset. These examples of electrographic seizures were recorded by the RNS System during the prestimulation baseline in patients with a lead in/over: (**A**) right frontal motor cortex; (**B**) left lateral temporal lobe; (**C**) right parietal lobe; and (**D**) left lateral occipital lobe. Spectrograms plot the power of the ECoG signal at given frequencies over time (top panel) and time series data for the ECoG are shown below each spectrogram. © 2017 NeuroPace, Inc.
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related mild or serious AEs related to language or speech. One patient with occipital leads reported a transient experience of brief star-like events (mild) that resolved when the stimulation current was decreased. Two of the patients who were classified as having frontal onsets and two as having multilobar onsets had at least one lead targeted to the insular cortex. The LOCF seizure changes for these patients were −98%, −96%, −92%, and 10%. There were no mild or serious adverse events related to autonomic function in any of the patients receiving stimulation in the insula.

Discussion

This study provides extensive data on patients with medically intractable partial seizures arising from neocortex that were treated with brain-responsive stimulation. There were acute and long-term improvements in seizure control, and the stimulation parameters necessary to achieve meaningful seizure reduction did not cause repeated or sustained deficits in neurologic function in any lobe of the neocortex. There were no serious AEs related to stimulation of eloquent cortex. Rates of infection were well within the expected range for implantation of intracranial electrodes for localization of the seizure focus for epilepsy resective surgery[13–17] and for implantation of a deep brain stimulator for movement disorders[18] or for epilepsy.[19]

Patients who had been treated previously with surgical resection or VNS were as likely to do well as patients who had not. The preponderance of patients in this series had intracranial monitoring for localization of the seizure focus, and there was no difference in seizure reduction between patients who did and did not have this monitoring. Of note, the majority of patients who did not have intracranial monitoring had a lesion on imaging. The very small number of nonlesional patients who did not have intracranial monitoring precludes drawing meaningful conclusions about the benefits of intracranial monitoring in this series.[20]

The only demographic characteristic that identified patients who were more likely to respond was the presence of structural lesion on magnetic resonance imaging (MRI). Although both lesional and nonlesional patients benefited from responsive therapy, seizure reduction was greater in patients who had a structural lesion. Similarly, studies of surgical outcomes in patients with focal-onset seizures have also reported better outcomes in patients who have a lesion corresponding to the seizure focus than in those who have nonlesional epilepsy.[2,21–23] It is possible that localization of the seizure focus was less precise in patients without a structural lesion. However, these patients still had a 45% reduction in seizures. Because brain-responsive neurostimulation is a nondestructive therapy, the risk of cognitive or functional deficits for patients without a lesion remains low, which indicates a favorable risk–reward profile for this population.

Although some patients can achieve seizure freedom with cortical resections,[24–27] in many instances, a full resection of

the epileptogenic onset zone is not possible because of the risk of functional deficits. For example, in one series, although 31% of patients who had resections in motor areas were seizure-free, 23% had new, severe postoperative deficits.[5] Another series reported that 57% of patients with parietal onsets achieved seizure freedom but 30% developed Gerstmann syndrome.[6] A report of patients undergoing resections of occipital lobe seizure foci found that 71% were seizure-free, but 39% reported new visual field defects.[28] Although treatment with brain-responsive neurostimulation is less likely to result in seizure freedom than treatment with epilepsy surgery, substantial seizure reductions were achieved and several patients achieved extended periods without seizures. Baseline assessments for the RNS System trials were limited to 3 months, and thus whether a patient had a prior history of extended periods of seizure freedom is unknown. However, patients entering the trials were required to have uncontrolled seizures at the time of enrollment. In addition, many of these patients had failed to achieve seizure control not only with medications, but also with prior resections and VNS. The seizure reductions achieved with brain-responsive stimulation did not occur at the expense of cognitive or neurologic function. Furthermore, patients treated with brain-responsive stimulation in eloquent cortex did not have implant- or stimulation-related functional deficits.

In fact, Loring et al.,[29] reported that patients with neocortical onsets who participated in the Pivotal trial (n = 76) demonstrated statistically significant improvements in naming, with 32% meeting criteria for reliable change.[29] These patients also showed statistically significant improvements in visual memory and executive function. Likewise, they reported improvements in all domains of quality of life (epilepsy-targeted, cognitive, mental health, and physical health), and 51% reported clinically meaningful improvements in overall quality of life.[30]

There are limitations to this analysis of open-label data from the RNS System trials. The trials were not powered to provide an estimate of the effect size (i.e., seizure reduction) in subsets of patients, as evidenced by the relatively large IQR. More data are needed to accurately estimate effect size. Whether a patient was categorized as having a structural lesion was based on physician report, rather than on a standardized MRI protocol or histopathology. Based on the data collected in the clinical trials, it is not possible to know whether changes in any one antiepileptic drug (AED) affected seizure outcomes, since investigators in the trial were able to adjust AEDs as needed for management of their patients' epilepsy. However, previously published data that includes data from the patients in this series indicate that seizure response in patients whose AEDs remained stable was similar to that of patients who had AEDs added or decreased.[11]

An additional limitation to the current analysis is that, as with all new epilepsy therapies, the outcomes of the RNS System clinical trials were dependent on patient-reported seizure diary data. Recent studies conducted in the epilepsy monitoring unit have indicated that patients are not aware of >50% of their complex partial and secondarily generalized tonic–clonic seizures.[31,32] Although the seizure diary remains the gold standard for epilepsy trials and seizure diary estimates of seizure frequency have been found to be consistent across time,[33] an objective measure of disease frequency and severity would be beneficial, and analyses of the RNS System data are underway.

It could be that the patients who did not respond to stimulation therapy did not have optimal lead placement or stimulation settings. It is not known whether stimulation needs to be delivered directly at the seizure focus,[34] near the focus, or in relevant propagation pathways or networks. In addition, although patients with MRI-identified lesions tended to respond well to stimulation, it is uncertain from the current study how the type and volume of a lesion may impact outcome. Additional clinical data will be necessary to provide the opportunity to assess whether MRI and functional neuroimaging studies such as magnetoencephalography (MEG), single-photon emission tomography (SPECT), and positron emission tomography (PET) can help refine patient selection and guide lead placement to improve efficacy. In the future, alternative stimulation strategies, such as low-frequency stimulation and longer duration pulses can be evaluated to increase efficacy in those patients who do not respond to high-frequency, short-burst stimulation.[35] Moreover, understanding the volume of tissue activated by the different stimulation approaches may help guide the personalization of the therapy for individual patients.

One third of patients with partial-onset seizures do not respond optimally to medications, and although many are candidates for focal cortical resections,[15] results of surgery in patients with seizures arising from neocortical areas are less encouraging than those in patients with seizures originating from the mesial temporal lobe.[36,37] One possible explanation for this is that a neocortical epileptic focus is more difficult to localize than a mesial temporal seizure focus. Another reason for surgical failure is that a full resection of the seizure focus may not be possible because of the risk of functional deficit.[38] Nondestructive therapies such as responsive neurostimulation may be an option for these patients. The benefit of responsive stimulation in patients with seizure onsets in the neocortex is achieved with stimulation settings that are below the perceptual threshold in almost every case. In addition, there are no known chronic stimulation-related side effects. This experience supports brain-responsive neurostimulation as a treatment option for adults with partial-onset seizures arising from any region of the neocortex, including eloquent cortex.

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References

1. Jobst BC, Cascino GD. Resective epilepsy surgery for drug-resistant focal epilepsy: a review. *JAMA* 2015;313:285–293.
2. Téllez-Zenteno JF, Hernández Ronquillo L, Moien-Afshari F, et al. Surgical outcomes in lesional and non-lesional epilepsy: a systematic review and meta-analysis. *Epilepsy Res* 2010;89:310–318.

3. Pondal-Sordo M, Diosy D, Téllez-Zenteno JF, et al. Epilepsy surgery involving the sensory-motor cortex. *Brain J Neurol* 2006;129:3307–3314.
4. Kim Y-H, Kim CH, Kim JS, et al. Risk factor analysis of the development of new neurological deficits following supplementary motor area resection. *J Neurosurg* 2013;119:7–14.
5. Ljunggren S, Andersson-Roswall L, Rydenhag B, et al. Cognitive outcome two years after frontal lobe resection for epilepsy–a prospective longitudinal study. *Seizure* 2015;30:50–56.
6. Binder DK, Podlogar M, Clusmann H, et al. Surgical treatment of parietal lobe epilepsy. *J Neurosurg* 2009;110:1170–1178.
7. von Lehe M, Wellmer J, Urbach H, et al. Epilepsy surgery for insular lesions. *Rev Neurol (Paris)* 2009;165:755–761.
8. Tandon N, Alexopoulos AV, Warbel A, et al. Occipital epilepsy: spatial categorization and surgical management. *J Neurosurg* 2009;110:306–318.
9. Morrell MJ; RNS System in Epilepsy Study Group. Responsive cortical stimulation for the treatment of medically intractable partial epilepsy. *Neurology* 2011;77:1295–1304.
10. Bergey GK, Morrell MJ, Mizrahi EM, et al. Long-term treatment with responsive brain stimulation in adults with refractory partial seizures. *Neurology* 2015;84:810–817.
11. Heck CN, King-Stephens D, Massey AD, et al. Two-year seizure reduction in adults with medically intractable partial onset epilepsy treated with responsive neurostimulation: final results of the RNS System Pivotal trial. *Epilepsia* 2014;55:432–441.
12. Zeger SL, Liang KY. Longitudinal data analysis for discrete and continuous outcomes. *Biometrics* 1986;42:121–130.
13. Wong CH, Birkett J, Byth K, et al. Risk factors for complications during intracranial electrode recording in presurgical evaluation of drug resistant partial epilepsy. *Acta Neurochir (Wien)* 2009;151:37–50.
14. Behrens E, Schramm J, Zentner J, et al. Surgical and neurological complications in a series of 708 epilepsy surgery procedures. *Neurosurgery* 1997;41:1–10.
15. Engel J, Wiebe S, French J, et al. Practice parameter: temporal lobe and localized neocortical resections for epilepsy: report of the Quality Standards Subcommittee of the American Academy of Neurology, in association with the American Epilepsy Society and the American Association of Neurological Surgeons. *Neurology* 2003;60:538–547.
16. Silberbusch MA, Rothman MI, Bergey GK, et al. Subdural grid implantation for intracranial EEG recording: CT and MR appearance. *AJNR Am J Neuroradiol* 1998;19:1089–1093.
17. Spencer SS, Spencer DD, Williamson PD, et al. Combined depth and subdural electrode investigation in uncontrolled epilepsy. *Neurology* 1990;40:74–79.
18. Weaver FM, Follett K, Stern M, et al. Bilateral deep brain stimulation vs best medical therapy for patients with advanced Parkinson disease: a randomized controlled trial. *JAMA* 2009;301:63–73.
19. Salanova V, Witt T, Worth R, et al. Long-term efficacy and safety of thalamic stimulation for drug-resistant partial epilepsy. *Neurology* 2015;84:1017–1025.
20. Noe K, Sulc V, Wong-Kisiel L, et al. Long-term outcomes after nonlesional extratemporal lobe epilepsy surgery. *JAMA Neurol* 2013;70:1003–1008.
21. Cohen-Gadol AA, Wilhelmi BG, Collignon F, et al. Long-term outcome of epilepsy surgery among 399 patients with nonlesional seizure foci including mesial temporal lobe sclerosis. *J Neurosurg* 2006;104:513–524.
22. Englot DJ, Wang DD, Rolston JD, et al. Rates and predictors of long-term seizure freedom after frontal lobe epilepsy surgery: a systematic review and meta-analysis. *J Neurosurg* 2012;116:1042–1048.
23. Hakimian S, Kershenovich A, Miller JW, et al. Long-term outcome of extratemporal resection in posttraumatic epilepsy. *Neurosurg Focus* 2012;32:E10.
24. Salanova V, Andermann F, Olivier A, et al. Occipital lobe epilepsy: electroclinical manifestations, electrocorticography, cortical stimulation and outcome in 42 patients treated between 1930 and 1991. Surgery of occipital lobe epilepsy. *Brain J Neurol* 1992;115(Pt 6):1655–1680.
25. Salanova V, Andermann F, Rasmussen T, et al. Parietal lobe epilepsy. Clinical manifestations and outcome in 82 patients treated surgically between 1929 and 1988. *Brain J Neurol* 1995;118(Pt 3):607–627.
26. Williamson PD, Thadani VM, Darcey TM, et al. Occipital lobe epilepsy: clinical characteristics, seizure spread patterns, and results of surgery. *Ann Neurol* 1992;31:3–13.
27. Williamson PD, Boon PA, Thadani VM, et al. Parietal lobe epilepsy: diagnostic considerations and results of surgery. *Ann Neurol* 1992;31:193–201.
28. Yang P-F, Jia Y-Z, Lin Q, et al. Intractable occipital lobe epilepsy: clinical characteristics, surgical treatment, and a systematic review of the literature. *Acta Neurochir (Wien)* 2015;157:63–75.
29. Loring DW, Kapur R, Meador KJ, et al. Differential neuropsychological outcomes following targeted responsive neurostimulation for partial-onset epilepsy. *Epilepsia* 2015;56:1836–1844.
30. Meador KJ, Kapur R, Loring DW, et al. Quality of life and mood in patients with medically intractable epilepsy treated with targeted responsive neurostimulation. *Epilepsy Behav* 2015;45:242–247.
31. Poochikian-Sarkissian S, Tai P, del Campo M, et al. Patient awareness of seizures as documented in the epilepsy monitoring unit. *Can J Neurosci Nurs* 2009;31:22–23.
32. Fisher RS, Blum DE, DiVentura B, et al. Seizure diaries for clinical research and practice: limitations and future prospects. *Epilepsy Behav* 2012;24:304–310.
33. Glueckauf RL, Girvin JP, Braun JR, et al. Consistency of seizure frequency estimates across time, methods, and observers. *Health Psychol* 1990;9:427–434.
34. Motamedi GK, Lesser RP, Miglioretti DL, et al. Optimizing parameters for terminating cortical afterdischarges with pulse stimulation. *Epilepsia* 2002;43:836–846.
35. Koubeissi MZ, Kahriman E, Syed TU, et al. Low-frequency electrical stimulation of a fiber tract in temporal lobe epilepsy. *Ann Neurol* 2013;74:223–231.
36. Englot DJ, Chang EF. Rates and predictors of seizure freedom in resective epilepsy surgery: an update. *Neurosurg Rev* 2014;37:389–405.
37. Chen H, Modur PN, Barot N, et al. Predictors of postoperative seizure recurrence: a longitudinal study of temporal and extratemporal resections. *Epilepsy Res Treat* 2016;2016:7982494.
38. Yun C-H, Lee SK, Lee SY, et al. Prognostic factors in neocortical epilepsy surgery: multivariate analysis. *Epilepsia* 2006;47:574–579.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Patient disposition. Flowchart showing the progression of patients through the RNS System clinical trials.