


## FULL-LENGTH ORIGINAL RESEARCH



# Brain-responsive neurostimulation in patients with medically intractable mesial temporal lobe epilepsy

<sup>1</sup>Eric B. Geller, <sup>2</sup>Tara L. Skarpaas, <sup>3</sup>Robert E. Gross, <sup>4</sup>Robert R. Goodman, <sup>5</sup>Gregory L. Barkley, <sup>6</sup>Carl W. Bazil, <sup>7</sup>Michael J. Berg, <sup>8</sup>Gregory K. Bergey, <sup>9</sup>Sydney S. Cash, <sup>9</sup>Andrew J. Cole , <sup>10</sup>Robert B. Duckrow, <sup>11</sup>Jonathan C. Edwards, <sup>12</sup>Stephan Eisenschenk, <sup>7</sup>James Fessler, <sup>13</sup>Nathan B. Fountain, <sup>14</sup>Alicia M. Goldman, <sup>15</sup>Ryder P. Gwinn, <sup>16</sup>Christianne Heck, <sup>17</sup>Aamar Herekar, <sup>10</sup>Lawrence J. Hirsch, <sup>18</sup>Barbara C. Jobst, <sup>19</sup>David King-Stephens, <sup>20</sup>Douglas R. Labar, <sup>21</sup>James W. Leiphart, <sup>22</sup>W. Richard Marsh, <sup>23</sup>Kimford J. Meador, <sup>14</sup>Eli M. Mizrahi, <sup>24</sup>Anthony M. Murro, <sup>25</sup>Dileep R. Nair, <sup>26</sup>Katherine H. Noe, <sup>24</sup>Yong D. Park, <sup>27</sup>Paul A. Rutecki, <sup>28</sup>Vicenta Salanova, <sup>29</sup>Raj D. Sheth, <sup>30</sup>Donald C. Shields, <sup>31</sup>Christopher Skidmore, <sup>32</sup>Michael C. Smith, <sup>33</sup>David C. Spencer, <sup>6</sup>Shraddha Srinivasan, <sup>34</sup>William Tatum, <sup>14</sup>Paul C. Van Ness, <sup>35</sup>David G. Vossler, <sup>34</sup>Robert E. Wharen Jr, <sup>22</sup>Gregory A. Worrell, <sup>14</sup>Daniel Yoshor, <sup>26</sup>Richard S. Zimmerman, <sup>2</sup>Kathy Cicora, <sup>2</sup>Felice T. Sun, and <sup>2,23</sup>Martha J. Morrell

*Epilepsia*, 58(6):994–1004, 2017

doi: 10.1111/epi.13740

## SUMMARY

**Objective:** Evaluate the seizure-reduction response and safety of mesial temporal lobe (MTL) brain-responsive stimulation in adults with medically intractable partial-onset seizures of mesial temporal lobe origin.

**Methods:** Subjects with mesial temporal lobe epilepsy (MTLE) 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.

**Results:** There were 111 subjects with MTLE; 72% of subjects had bilateral MTL onsets and 28% had unilateral onsets. Subjects had one to four leads placed; only two leads could be connected to the device. Seventy-six subjects had depth leads only, 29 had both depth and strip leads, and 6 had only strip leads. The mean follow-up was 6.1 ± (standard deviation) 2.2 years. The median percent seizure reduction was 70% (last observation carried forward). Twenty-nine percent of subjects experienced at least one seizure-free period of 6 months or longer, and 15% experienced at least one seizure-free period of 1 year or longer. There was no difference in seizure reduction in subjects with and without mesial temporal sclerosis (MTS), bilateral MTL onsets, prior resection, prior intracranial monitoring, and prior vagus nerve stimulation. In addition, seizure reduction was not dependent on the location of depth leads relative to the hippocampus. The most frequent serious device-related adverse event was soft tissue implant-site infection (overall rate, including events categorized as device-related, uncertain, or not device-related: 0.03 per implant year, which is 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 patients with unilateral or bilateral MTLE who are not candidates for temporal lobectomy or who have failed a prior MTL resection.

**KEY WORDS:** Closed-loop, Neuromodulation, Partial seizures, Hippocampus, Focal stimulation.



Dr. Eric Geller is Director, Adult Comprehensive Epilepsy Center at Saint Barnabas Medical Center.

## KEY POINTS

- Responsive stimulation is a well-tolerated treatment option for patients with MTL who are not candidates for a temporal lobe resection
- Median seizure reductions were 70% using a last observation carried forward analysis
- Twenty-nine percent of patients reported periods of seizure freedom lasting  $\geq 6$  months and 15% reported seizure-free periods  $\geq 1$  year
- Seizure reductions were not dependent on any clinical characteristics including MTS, bilateral onsets, prior resection, and prior VNS
- Seizure reductions were similar in patients with depth leads placed within or adjacent to the hippocampus

Temporal lobectomy is the most effective treatment for many patients with medically intractable mesial temporal lobe epilepsy (MTLE). However, 25–35% of patients with MTL who are treated with resective or ablative surgeries do not achieve sustained seizure freedom, and others are not candidates for surgery because the risks, particularly to memory or language, are too high.<sup>1–5</sup> Neuromodulation therapies are a treatment option for some of these patients.

Brain-responsive (closed-loop) neurostimulation (RNS System) is a safe and effective adjunctive treatment to reduce the frequency of seizures in medically refractory adults with partial-onset seizures.<sup>6–8</sup> However, the results specific to subjects with MTL have not been published previously.

This report provides an analysis of the long-term results of responsive MTL stimulation in subjects with MTL participating in the RNS System clinical trials. This experience may assist physicians when counseling patients who are considering or being treated with brain-responsive stimulation.

## METHODS

The RNS System (NeuroPace, Mountain View, CA, U.S.A.) provides brain-responsive stimulation directly to one or two seizure foci when abnormal electrocorticographic (ECoG) activity is detected. A cranially implanted programmable neurostimulator is connected to one or two depth or cortical strip leads that are surgically placed at one or two previously identified seizure foci. Each lead contains four electrode contacts. The neurostimulator continually senses ECoG activity and is programmed by the physician to detect specific ECoG patterns, typically abnormal activity that has been observed at the onset of electrographic seizures. Once detection settings are refined for a patient, the neurostimulator is programmed to deliver brief stimulus pulses through the electrodes in response to detections. In addition, the neurostimulator stores ECoG samples. The physician continues to adjust detection and stimulation parameters as needed for each patient.

The study protocols have been described elsewhere.<sup>6–8</sup> A largely open-label Feasibility study assessed safety and followed adults with medically refractory partial-onset epilepsy over a 3-month preimplantation baseline and a 2-year postimplantation treatment period. A randomized controlled trial (Pivotal study) enrolled adults with medically intractable partial epilepsy and an average of three or more partial seizures per month. A 3-month baseline was followed by a 1-month postimplantation stabilization period and then by a 4-month blinded period during which subjects were randomized 1:1 to receive active or sham stimulation. All subjects received active stimulation in a subsequent open-label period to collect safety and efficacy data to 2 years postimplantation. Once subjects completed either the Feasibility or Pivotal study, they could continue in a 7-year follow-on Long-term Treatment (LTT) study. The study was ongoing as of the data cutoff on November 1, 2014.

Accepted March 3, 2017; Early View publication 11 April 2017.

<sup>1</sup>Saint Barnabas Health, Livingston, New Jersey, U.S.A.; <sup>2</sup>NeuroPace, Inc., Mountain View, California, U.S.A.; <sup>3</sup>Emory University, Atlanta, Georgia, U.S.A.; <sup>4</sup>Saint Luke's Hospital, New York City, New York, U.S.A.; <sup>5</sup>Henry Ford Hospital, Detroit, Michigan, U.S.A.; <sup>6</sup>Columbia University Medical Center, New York City, New York, U.S.A.; <sup>7</sup>University of Rochester Medical Center, Rochester, New York, U.S.A.; <sup>8</sup>Johns Hopkins University, Baltimore, Maryland, U.S.A.; <sup>9</sup>Massachusetts General Hospital, Boston, Massachusetts, U.S.A.; <sup>10</sup>Yale School of Medicine, New Haven, Connecticut, U.S.A.; <sup>11</sup>Medical University of South Carolina, Charleston, South Carolina, U.S.A.; <sup>12</sup>University of Florida College of Medicine, Gainesville, Florida, U.S.A.; <sup>13</sup>University of Virginia, Charlottesville, Virginia, U.S.A.; <sup>14</sup>Baylor College of Medicine, Houston, Texas, U.S.A.; <sup>15</sup>Swedish Medical Center, Seattle, Washington, U.S.A.; <sup>16</sup>University of Southern California, Los Angeles, California, U.S.A.; <sup>17</sup>Via Christi Clinic, Wichita, Kansas, U.S.A.; <sup>18</sup>Dartmouth-Hitchcock Medical Center, Lebanon, New Hampshire, U.S.A.; <sup>19</sup>California Pacific Medical Center, San Francisco, California, U.S.A.; <sup>20</sup>Weill Cornell Medicine, New York City, New York, U.S.A.; <sup>21</sup>Inova Medical Group, Fairfax, Virginia, U.S.A.; <sup>22</sup>Mayo Clinic College of Medicine, Rochester, Minnesota, U.S.A.; <sup>23</sup>Stanford University School of Medicine, Stanford, California, U.S.A.; <sup>24</sup>Augusta University, Augusta, Georgia, U.S.A.; <sup>25</sup>Cleveland Clinic, Cleveland, Ohio, U.S.A.; <sup>26</sup>Mayo Clinic College of Medicine, Scottsdale, Arizona, U.S.A.; <sup>27</sup>University of Wisconsin, Madison, Wisconsin, U.S.A.; <sup>28</sup>Indiana University, Indianapolis, Indiana, U.S.A.; <sup>29</sup>Nemours Foundation, Jacksonville, Florida, U.S.A.; <sup>30</sup>George Washington University School of Medicine & Health Sciences, Washington, Washington DC, U.S.A.; <sup>31</sup>Thomas Jefferson University, Philadelphia, Pennsylvania, U.S.A.; <sup>32</sup>Rush University Medical Center, Chicago, Illinois, U.S.A.; <sup>33</sup>Oregon Health & Science University, Portland, Oregon, U.S.A.; <sup>34</sup>Mayo Clinic College of Medicine, Jacksonville, Florida, U.S.A.; and <sup>35</sup>Valley Medical Center, Renton, Washington, U.S.A.

Address correspondence to Tara L. Skarpaas, 455 N. Bernardo Ave, Mountain View, CA 94043, U.S.A. E-mail: tskarpaas@neuropace.com

© 2017 The Authors. *Epilepsia* published by Wiley Periodicals, Inc. on behalf of International League Against Epilepsy.

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

## SUBJECTS

Subjects with MTLE who participated in clinical trials of the RNS System were included in the analyses. Study protocols were approved by the institutional review boards of participating investigation sites. All subjects provided written informed consent. The studies were registered on [www.clinicaltrials.gov](http://www.clinicaltrials.gov) (NCT00079781, NCT00264810, and NCT00572195).

### Long-term seizure reduction

Long-term results over years 2–6 postimplantation were measured as median percent change in seizures and responder rate (the percentage of subjects with a 50% or greater reduction in seizures) for each 3-month period compared to the preimplantation baseline. Seizure data were collected using seizure diaries.

In addition, last observation carried forward (LOCF) analyses based on the most recent 3 months of available open-label seizure diary data for each subject were performed. This ensured that the results were not influenced by subjects who discontinued or those who had not yet completed 6 years of follow-up.

### Long-term seizure reduction by demographic characteristics

Seizure reduction was compared for subjects with bilateral and unilateral MTL seizure onsets, and according to prespecified characteristics that could potentially affect the clinical response to treatment. These included whether the subject had mesial temporal sclerosis (MTS), had intracranial monitoring for localization, or had been treated with vagus nerve stimulation (VNS) or temporal lobectomy. A logistic generalized estimating equation (GEE) model was fit to the results for mean percent change for each 3-month period from the beginning of year 2 through the end of year 6 for each of the comparisons. GEE is an extension of generalized linear modeling that handles missing data and properly assigns significance to multiple correlated measurements. The percent change in seizure rate for all available 3-month epochs was analyzed using a GEE model with a compound symmetric correlation structure.<sup>9</sup> *p*-Values were based on empirical standard errors. For all comparisons,  $\alpha$  was set to  $p < 0.05$ . In addition, median percent change and responder rate using LOCF were calculated for each clinical characteristic.

### Depth lead placement

Depth lead location relative to the hippocampus was determined for subjects with preimplantation magnetic resonance imaging (MRI) and postimplantation computed tomography (CT) coregistered images. The coregistered images were reviewed by two independent neurosurgeons who categorized a depth lead as within the hippocampus if

at least two of the four electrode contacts were in the hippocampus, and outside of the hippocampus if more than two of the four contacts were not in the hippocampus. Seizure reduction was assessed using the GEE and LOCF analysis methods described earlier.

### Long-term Safety

Safety was assessed as the rate and types of spontaneously reported serious and mild adverse events (AEs)<sup>8</sup> and classified by the investigator as device related (definitely or potentially related to the RNS System) or not. An independent Data Monitoring Committee reviewed all AEs and a second committee determined whether deaths met criteria for sudden unexpected death in epilepsy (SUDEP).

## RESULTS

There were 111 subjects with MTLE treated with responsive stimulation during the Feasibility ( $N = 16$ ) and Pivotal ( $N = 95$ ) studies, and 102 subjects continued into the LTT study. Subject accountability and reasons for discontinuation are provided in Figure 1. The mean follow-up at the time of data cutoff was  $6.1 \pm$  (standard deviation) 2.2 years, and the accumulated experience was 671 patient implant years and 631 patient years during which responsive MTL stimulation was provided.

### Demographic characteristics

Demographic characteristics are provided in Table 1. Most subjects had frequent seizures for many years and had failed treatment with multiple antiepileptic medications and in some cases VNS (24%) or temporal lobectomy (12%). MTS was present in 55% of subjects. Ictal onsets were bilateral in 72% of subjects and unilateral in 28% (68% left; 32% right). Sixty percent of subjects with unilateral right onsets had undergone a temporal lobectomy (three right; three left).

### Lead placement approaches

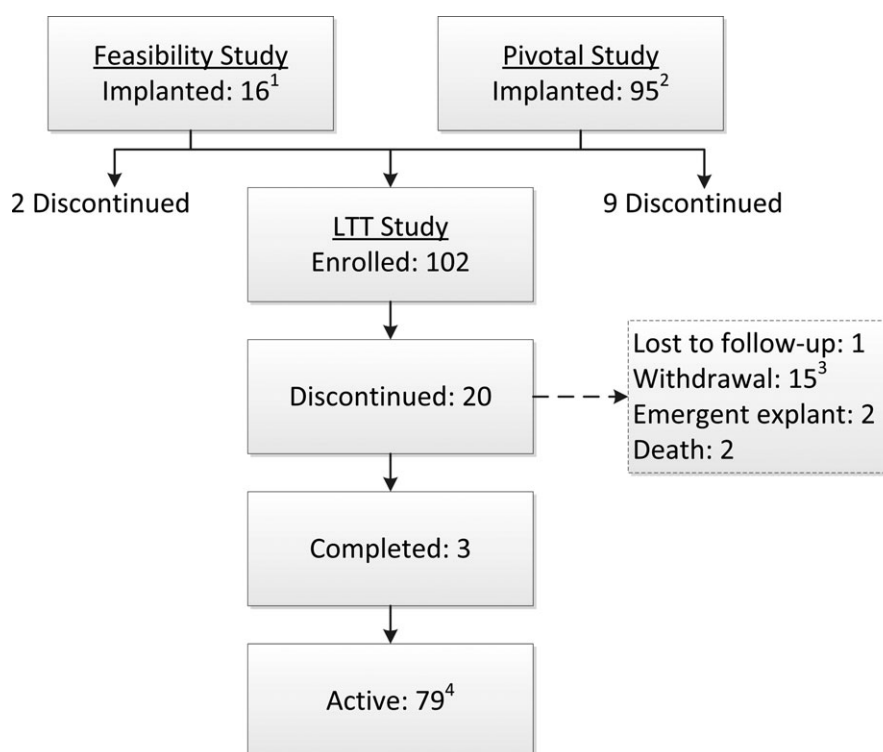
Subjects had one to four leads placed during the initial procedure: one lead ( $n = 1$ ); two leads ( $n = 92$ ); three leads ( $n = 4$ ); and four leads ( $n = 14$ ). Only two depth leads could be implanted and only two leads of any type could be connected to the device at a time. Seventy-six subjects had only depth leads placed, 29 had both depth and strip leads, and 6 had only strip leads. Most depth leads were implanted along the longitudinal axis of the hippocampus. Cortical strip leads were typically placed subtemporally. CT scans showing common lead implantation strategies are provided in Figure 2(A–C).

Of the 13 subjects with a prior temporal lobectomy, leads were contralateral ( $n = 6$ ), ipsilateral ( $n = 2$ ), or both ( $n = 5$ ) to the resection. All subjects had at least one depth lead.

**Figure 1.**

Subject Progression.<sup>1</sup>Two subjects discontinued prior to completing the study. <sup>2</sup>Nine subjects discontinued prior to completing the study; two of those subjects subsequently enrolled in the Long-term Treatment study. <sup>3</sup>Reasons for withdrawal: to pursue other treatments (2); subject chose not to replace neurostimulator after expected battery depletion (4); insufficient efficacy (2); subject chose not to replace neurostimulator after resolution of infection (2); transfer of medical care at nonstudy center (1); non-compliance (3); ongoing suicidality/noncompliance (1). <sup>4</sup>Study ongoing; data as of November 1, 2014.

*Epilepsia* © ILAE

**Table 1. Subject demographics and characteristics.**

Characteristic	Mean ± SD (range) or % (n/N)
Female	48% (53/111)
Age in years <sup>a</sup>	37.3 ± 11.3 (18–60)
Duration of epilepsy in years <sup>a</sup>	19.8 ± 12.7 (2–57)
Number of AEDs <sup>a</sup>	2.7 ± 1.1 (1–6)
Baseline monthly seizure frequency	15.1 ± 25.0 (1–217) <sup>b</sup> median = 7.7
Prior intracranial monitoring	46% (51/111)
Prior epilepsy surgery	12% (13/111)
Prior treatment with VNS	24% (27/111)
Bilateral MTL seizure onsets	72% (80/111)
Unilateral MTL seizure onsets	28% (31/111)
Left unilateral MTL	68% (21/31)
Right unilateral MTL	32% (10/31)
Mesial temporal sclerosis	55% (61/111)

<sup>a</sup>At enrollment in originating study.

<sup>b</sup>The lower end of the monthly seizure range was for a single subject in the RNS Feasibility Study who enrolled based on simple partial sensory seizures and did not have other disabling seizures during the baseline period. AEDs, antiepileptic medications; VNS, vagus nerve stimulation.

Sixty-two of the subjects had coregistered MRI and CT images with sufficient resolution for localizing the depth leads. In 31 subjects, at least one depth lead was positioned in the hippocampus. The remaining 31 subjects had depth leads near but not within the hippocampus. Figure 2(D–E) shows bilateral depth lead placements in two subjects; one with leads within the hippocampus and one with leads ventral to the hippocampus.

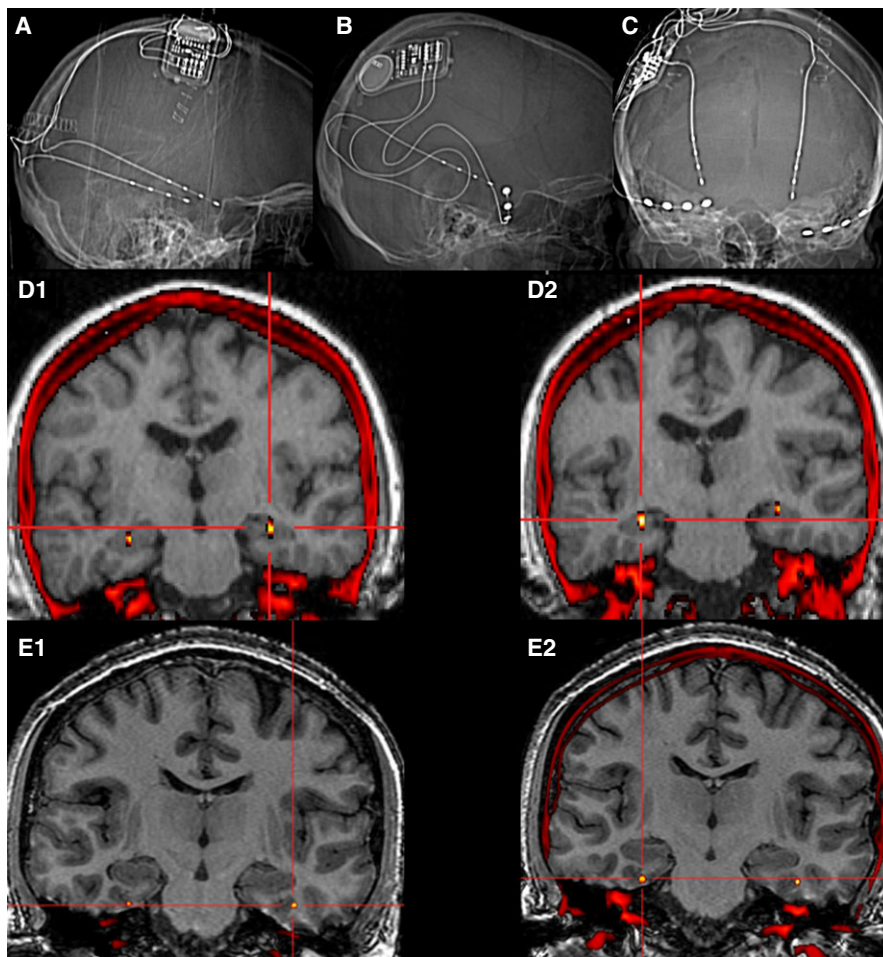
Figure 3 shows representative ECoG recordings from MTL subjects. Stimulation was commonly delivered to hypersynchronous and low-voltage fast electrographic activity. Typical stimulation settings were: 1.5–2.5  $\mu\text{C}/\text{cm}^2$  (range 0.1–19.0  $\mu\text{C}/\text{cm}^2$ ); 1.0–3.0 mA (range 0.5–12.0 mA); 200 Hz (range 1–333 Hz); 160  $\mu\text{sec}$  pulse width (range 80–1000  $\mu\text{sec}$ ); and 100 msec burst duration (range 10–5,000 msec). The median number of programming changes from the beginning of the second-year postimplantation to the end of the data analysis period was 3 per year per subject (range 1–7). These programming changes included adjustments to stimulation, detection, or both.

### Long-term seizure reduction

The long-term response to treatment with MTL responsive stimulation is presented in Figure 4. Disabling seizures were reduced by a median 66.5% (interquartile range [IQR] 31.8–93.7%) at 6 years, and the 50% responder rate reached 64.6% (95% confidence interval [CI] 53.8–74.1%). Using LOCF, disabling seizures were reduced by a median of 70% (IQR 31.8–92.9%;  $n = 106$ ), and the responder rate was 66% (95% CI 56.6–74.4%). No seizures were reported by 20.8% of subjects in the last 3 months. Over the entire open-label period, 45% (50/111) of subjects reported seizure-free intervals lasting  $\geq 3$  months, 29%  $\geq 6$  months (32/111), and 15%  $\geq 1$  year (17/111).

There were no statistically significant differences, by GEE, in seizure reduction between subjects with and without MTS ( $p = 0.42$ ), between subjects with bilateral and





**Figure 2.**

Common RNS Lead placement strategies for mesial temporal lobe epilepsy. (A) Bilateral depth leads targeting the hippocampus. (B) A depth lead targeting the hippocampus and a cortical strip lead targeting the anterior subtemporal region in a subject with unilateral mesial temporal seizure onsets. (C) Bilateral depth and cortical strip leads. The depth leads target the hippocampal region bilaterally and are connected to the neurostimulator. The cortical strip leads targeted the subtemporal regions bilaterally but are not connected to the neurostimulator. (D1 & D2) Co-registered postoperative CT and preoperative MRI scan for an individual subject with bilateral depth leads that met the criteria for being classified as “in” the hippocampus. Cross-hairs identify an electrode within the left (D1) and right (D2) hippocampi. (E1 & E2) Co-registered postoperative CT and preoperative MRI scan for an individual subject with bilateral depth leads that met the criteria for being “out” and ventral to the hippocampus. Cross-hairs identify an electrode outside the left (E1) and right (E2) hippocampi.

*Epilepsia* © ILAE

unilateral onsets ( $p = 0.97$ ), between subjects localized with intracranial monitoring and those not ( $p = 0.15$ ), and between those treated and not treated previously with VNS ( $p = 0.78$ ) or epilepsy surgery ( $p = 0.54$ ). Table 2 provides the median percent change and responder rates using an LOCF analysis for each of the demographic characteristics.

In addition, there were no statistically significant differences in seizure reduction between subjects with at least one depth lead in the hippocampus and subjects with depth leads outside of the hippocampus (GEE,  $p = 0.9$ ). The LOCF median percent reduction in seizure rate was 77.8% (IQR 32.3–100%;  $n = 31$ ) for the hippocampal group and 60.2%

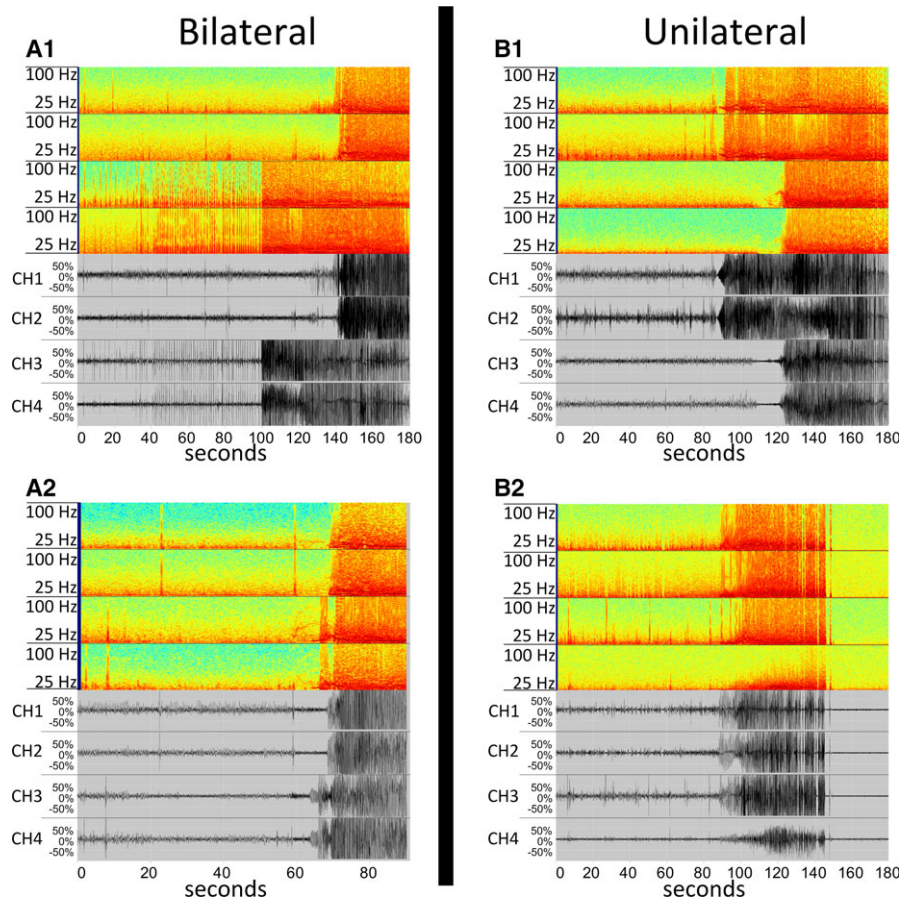
(IQR 29.9–87.8%;  $n = 31$ ) for the MTL extrahippocampal group. The LOCF responder rates were 67.7% (95% CI 50.1–81.4%) and 61.3% (95% CI 43.8–76.3%), respectively.

#### Device-related serious adverse events

There were only two device-related (related or uncertain as categorized by the investigator) serious adverse events (SAEs) that occurred in  $\geq 5\%$  of the 111 subjects over the 671 patient implant years. The SAEs were implant-site infection and device lead damage, described in detail in subsequent text.

**Figure 3.**

Representative time series and corresponding spectrograms demonstrating the electrocorticographic activity recorded by the RNS System in patients with bilateral and unilateral MTLE. **(A1)** Hypersynchronous high amplitude spike onset on channels 3 and 4 (right hippocampal depth) in a subject with bilateral MTLE and depth leads targeting the hippocampus bilaterally. **(A2)** Low voltage fast onset on channels 1 (left depth), 3 and 4 (right depth) in a second subject with bilateral MTLE and bilateral depth leads targeting the hippocampus. **(B1)** Electrographic seizure onset on channels 1 and 2 (left hippocampal depth) for a subject with unilateral MTLE. The event subsequently spreads to the lateral temporal subdural strip lead (channels 3 and 4). **(B2)** Electrographic seizure onset on both the strip (channels 1 and 2) and depth (channels 3 and 4) leads. *Epilepsia* © ILAE



### Implant-site infection

There were 15 SAEs (device-related or uncertain) occurring in 13 subjects (11.7%). All infections were superficial soft tissue only and there were no long-lasting neurologic or medical consequences. The implant-site infections occurred during the immediate postoperative period for three of the subjects; one had the neurostimulator and leads explanted. For the remaining subjects, the implant-site infection occurred beyond the immediate postoperative period; seven occurred within 3 months of a neurostimulator replacement. All subjects were treated with antibiotics; nine had their neurostimulator explanted, and six were later reimplanted.

In addition, two subjects experienced implant-site infections that were categorized as not device related. The infections occurred during the immediate postoperative period. Both were treated with antibiotics; one subject had the neurostimulator explanted and subsequently reimplanted.

Another two subjects experienced implant-site infections as a result of seizure-related injuries. Both subjects had their devices and leads explanted.

Finally, three SAEs related to implant-site skin erosion were reported in two subjects. Two events were reported in one subject; the events occurred over 7.5 years apart. The

first event resolved with antibiotics and surgical removal of the device, and the subject was reimplanted. However, the neurostimulator was explanted and not replaced following the second event. For the second subject, the SAE resolved with antibiotics and device removal. They were reimplanted with no further complications.

The overall rate of SAEs due to infection was 0.03 per patient implant year.

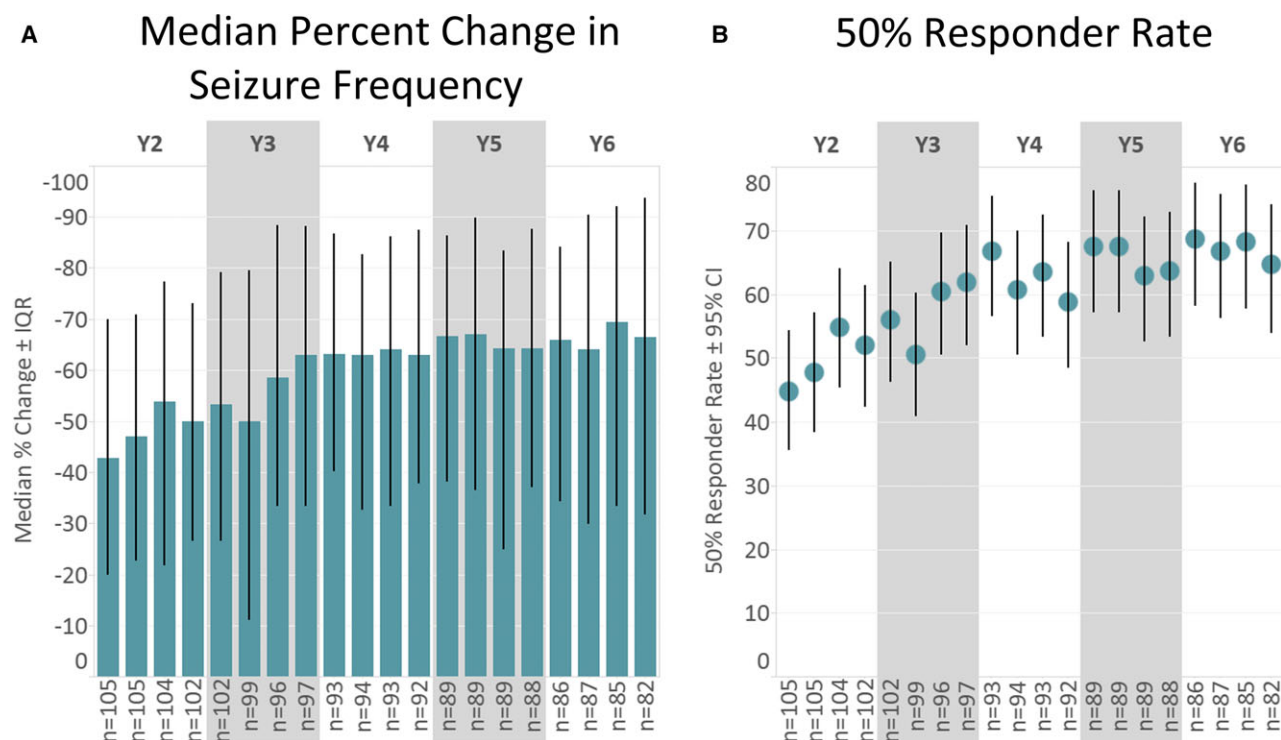
### Device lead damage

Seven subjects (6.3%) required lead replacement due to lead damage. The overall rate of SAEs due to lead damage was 0.01 per patient implant year.

### Other adverse events of interest

#### *Intracranial hemorrhage*

Three subjects (2.7%) had a serious AE related to intracranial hemorrhage (two were categorized as device-related). One was a CT-diagnosed asymptomatic intraventricular hemorrhage within the first days after bilateral depth-lead implant. The second subject sustained a subarachnoid hemorrhage following seizure-related head trauma. Neither of these events had any neurologic

**Figure 4.**

Long-term response to brain responsive stimulation in patients with MTL. (A) Median percent change in total disabling seizures in each 3-month bin beginning in Year 2 postimplantation. Error bars indicate interquartile ranges (25th–75th). (B) Responder Rate (percent of patients with a  $\geq 50\%$  reduction in total disabling seizures) in each 3-month bin beginning in Year 2 post-implantation. Error bars indicate 95% confidence intervals. © 2017 NeuroPace, Inc.

*Epilepsia* © ILAE

sequelae. The final subject had a subtemporal hematoma 2.5 years after implantation of two depth leads and two cortical strip leads. The subject experienced headaches that subsequently resolved.

In addition, one subject reported a mild AE related to a small postoperative subdural hematoma near the site of the neurostimulator and leads that resolved without intervention.

#### Death

There were 6 deaths in the 111 subjects over the 671 patient implant years and 631 patient stimulation years. One subject had a history of depression and died by suicide. Five deaths were attributed to possible ( $n = 2$ ), probable ( $n = 1$ ), or definite ( $n = 2$ ) SUDEP; two of these occurred while brain-responsive stimulation was off. Stimulation had been disabled in the first subject for  $>200$  days, and the second subject had not yet had stimulation enabled after the initial implant. None of the SUDEP events were deemed to be related to the device.

#### Photopsia

Transient mild AEs related to photopsia that were deemed to be related to the device or of uncertain device relation were reported in 16 subjects (14.4%). All but one

event resolved spontaneously or with changes to the stimulation parameters.

#### Memory impairment

Transient mild AEs related to memory impairment that were deemed to be related to the device or of uncertain device relation were reported in seven subjects (6.3%). All of these subjects had memory impairment on preimplant baseline neuropsychological assessment.

#### Depression

Two subjects (1.8%) reported transient SAEs related to depression with suicidal ideation that were deemed to be related to the device or of uncertain device relation. Both subjects had a prior history of depression and one had a prior history of a suicide attempt. In addition, as mentioned earlier, one MTL subject committed suicide during the trial. This subject also had a prior history of depression and suicidal ideation.

Mild AEs related to depression deemed to be of uncertain device relation were also reported in four subjects (3.6%). Two of the four subjects met criteria for moderate depression at baseline by validated mood inventory (Beck Depression Inventory-II; BDI-II) and/or reported a prior medical history of depression.



Table 2. LOCF by clinical demographic characteristic

Covariate		N	Median % change <sup>a</sup> (IQR)	Responder rate <sup>a</sup> (95% CI)
Prior intracranial monitoring	Yes	48	-74.5% (-29.2% to -95.4%)	66.7% (52.5% to 78.3%)
	No	58	-67.6% (-33.8% to -91%)	65.5% (52.7% to 76.4%)
Mesial temporal sclerosis	Yes	58	-60.6% (-30.5% to -89.2%)	60.3% (47.5% to 71.9%)
	No	48	-75.6% (-39.5% to -95.5%)	72.9% (59% to 83.4%)
Bilateral MTL onsets	Yes	75	-67.9% (-30% to -90%)	64.5% (53.3% to 74.3%)
	No	30	-72.5% (-37% to -95.9%)	70% (52.1% to 83.3%)
Prior epilepsy surgery	Yes	12 <sup>b</sup>	-72.5% (-57.4% to -93.5%)	91.7% (64.6% to 98.5%)
	No	95	-69.6% (-29.8% to -92.9%)	62.8% (52.7% to 71.9%)
Prior VNS	Yes	27	-56.8% (-27.5% to -81%)	63% (44.2% to 78.5%)
	No	78	-74.1% (-32.8% to -100%)	67.1% (56.1% to 76.4%)

IQR, Interquartile range, 25th to 75th percentile; VNS, vagus nerve stimulation.  
<sup>a</sup>Observed change in the most recent 3 months (LOCF).  
<sup>b</sup>Small n.

## DISCUSSION

Brain responsive MTL stimulation is a new treatment for patients with medically intractable MTLE who are not good resection candidates. Hippocampal stimulation in patients with MTLE has shown efficacy and good tolerability in several small series.<sup>10-20</sup> This is the first report of a large cohort of subjects treated with responsive mesial temporal stimulation.

In selected patients with medically intractable MTLE, anterior temporal lobectomy or amygdalohippocampectomy are often the procedures of choice, with long-term seizure-freedom rates of 60-75%.<sup>21</sup> Ablative procedures may also be an option for some.<sup>22</sup> However, many patients are not candidates for resective or ablative procedures. Seizures may arise from both temporal lobes or the risk to memory, language, or other neurologic functions is not acceptable. Many of the 111 subjects with medically refractory MTLE enrolled in the RNS System trials had bilateral MTL seizure onsets. Most of the subjects with unilateral onsets had seizures arising from the dominant temporal lobe and/or had already undergone a temporal lobectomy. Thus, the subjects included in the RNS System trials were not considered to be good surgical candidates.

Seizure reduction was substantial and sustained. Nearly half of the subjects experienced at least one  $\geq 3$ -month period without seizures, and 15% were without seizures for 1 year or longer. Treatment with responsive stimulation achieved reductions in seizure frequency reaching 70% over 6 years of prospective follow-up. This contrasts favorably with continued medical management in refractory nonsurgical candidate patients with MTLE, where sustained reductions in seizures are not typically observed.<sup>5,23</sup>

Seizure reductions for MTLE subjects who had intracranial monitoring were similar to those for subjects who did not. The criteria by which an individual epilepsy center chose to localize the seizure focus or foci were not standardized within the clinical trials. Therefore, no comment about the optimal localization testing to identify patients who

would benefit from responsive stimulation can be provided from this experience. However, intracranial monitoring was not required for subjects to achieve a good response. In fact, because it may take several weeks of chronic ambulatory monitoring to establish that a patient with MTLE has independent bilateral mesial temporal seizures,<sup>24</sup> there is a chance that lateralization of MTLE may not be adequate within a 1- to 2-week hospitalization for EEG monitoring, even with intracranial electrodes.

There was no difference in seizure reduction between subjects with and without MTS. The lack of a significant difference in seizure reduction contrasts with earlier reports by Velasco et al.,<sup>18</sup> in a small sample (n = 5 with MTS; n = 4 without) in which there was a greater and earlier reduction in seizures for MTLE patients with negative MRI findings. Future trials with standardized and sophisticated neuroimaging are required to better understand how neuroimaging might be used to optimize selection of patients for MTL responsive stimulation. In the short-term, however, patients with and without MTS can be considered candidates for responsive stimulation.

The experience with responsive MTL stimulation thus far suggests that leads need not be placed precisely within the hippocampus, since stimulation was as effective when MTL leads were placed within the hippocampus or nearby. Whether a larger volume of tissue activation was required for comparable seizure control when leads were outside the hippocampus was not assessed. However, these results are consistent with a smaller series in eight MTLE patients receiving hippocampal stimulation.<sup>11</sup> Decreases in epileptogenic activity were related to proximity of the active electrode(s) to the subiculum and not associated with the proximity of the active electrode(s) to the ictal focus. Future research will explore whether stimulation should be delivered directly to the seizure focus, near the focus, or in relevant propagation pathways or networks and will evaluate what volume of tissue activation may be required for each stimulation target. In addition, future research will also evaluate whether other techniques such as tractography or



intraoperative electrocorticography could provide insight into the ideal lead placement for an individual patient.

Responsive MTL stimulation was equally effective in subjects with bilateral or unilateral seizure onsets. There has been another report of successful treatment of bilateral as well as unilateral MTL seizures with direct brain stimulation.<sup>25</sup> This series also suggested that some patients with unilateral onsets who do not respond to unilateral MTL stimulation may improve when stimulation is provided bilaterally.

About one fourth of the MTLE subjects participating in the RNS System trials were previously treated with VNS. These subjects were as likely to benefit from responsive stimulation as the subjects who had not been treated with VNS. The mechanisms by which VNS and direct brain stimulation act to improve seizure control, while not completely understood, are likely quite different, suggesting that a failure to respond to one does not predict response to the other.

Some patients who have not achieved seizure control after temporal lobe resection may also be candidates for responsive MTL stimulation. Seizure reductions with responsive MTL stimulation in the RNS System trials were similar in both subjects who had and had not already undergone a MTL resection. However, it should be noted that the number of subjects with a prior resection was small, reducing the power of statistical comparisons. Some of the subjects with a prior temporal lobectomy were treated with responsive MTL stimulation ipsilateral to the resection with leads placed in residual MTL structures or at the margin of the resection; some were treated with MTL stimulation contralateral to the resection, and some were treated bilaterally. These findings suggest that responsive stimulation is an option if not all of the epileptogenic cortex can be resected. Furthermore, several case reports suggest that resective surgery and responsive stimulation can sometimes be used synergistically. Chronic ambulatory ECoG data collected by the RNS System has been used to identify patients in whom temporal resections would achieve seizure remission or substantial palliation. In some of these patients, responsive MTL stimulation was provided to the contralateral MTL.<sup>26,27</sup>

There are limitations to the analyses of the data provided. First the trials were not powered to provide assessments in subsets of subjects. Thus, more data will be necessary to confirm the comparisons of seizure reduction by clinical demographic characteristic. Second, the identification of subjects as having MTS was based on physician report and not a standardized imaging protocol. Furthermore, because subjects with MTS can have negative MRI findings and positive histopathology, some subjects with MTS may not have been identified. Finally, the data were collected as part of an open-label study and thus the effect of antiepileptic treatments cannot be clearly defined. However, analysis of seizure reduction in the trials indicated that there was no difference in seizure response between subjects whose

antiepileptic drugs (AEDs) remained stable and subjects who had AED modification.<sup>6,7</sup>

Surgical risks related to implantation of the RNS Neurostimulator and leads were well within the expected range for comparable procedures such as intracranial monitoring for localization of the seizure focus,<sup>6,28–30</sup> epilepsy surgery,<sup>5,21,31</sup> and deep brain stimulation for treatment of movement disorders<sup>32</sup> or epilepsy.<sup>33,34</sup> The most common device-related SAEs were implant-site infections, all of which were superficial soft tissue. The overall risk for an SAE related to infection per patient implant year was low. Perioperative hemorrhages occurred in 1.8% of subjects and were asymptomatic or caused only transient symptoms.

Long-term responsive MTL stimulation was cognitively and affectively well tolerated in these subjects with medically intractable MTLE, despite the high prevalence of moderate depression and suicidality at baseline. Meador et al.<sup>35</sup> reported that 19.4% of the MTLE subjects in the Pivotal study ( $n = 95$ ) met criteria for moderate depression at baseline and 10.8% endorsed suicidality.<sup>35</sup> These rates did not increase with treatment; the rates of depression and suicidality at 2 years were 16% and 12.6%, respectively.<sup>35</sup>

Across all 111 subjects (>671 implant years), device-related or device relation uncertain AEs related to memory were reported in 6.3%; however, all of these subjects had a preexisting memory impairment at baseline based on neuropsychological testing. Neuropsychological testing in the RNS System trials indicated that 56.8% of the Pivotal trial subjects ( $n = 95$ ) with MTLE had significant impairment in memory at baseline.<sup>36</sup> Loring et al.<sup>36</sup> reported that there were no cognitive declines with responsive MTL stimulation and that there were improvements in verbal memory, which, although small in magnitude, were statistically significant. A number of studies of open-loop hippocampal stimulation for temporal lobe epilepsy also found no adverse effects on memory.<sup>10–20</sup> The memory-sparing effects of MTL stimulation compare favorably to the progressive memory declines in patients with refractory MTL who continue to be treated with AEDs.<sup>37</sup> This also contrasts with cognitive outcomes following temporal lobectomy. Weighted estimates indicate a risk to verbal memory with left-sided temporal resection of 44%, and 20% for right-sided surgery.<sup>38</sup> Of course, risks to memory are weighed against the high likelihood of obtaining seizure freedom following temporal lobectomy.

During the Pivotal trial, the MTLE subjects treated with responsive stimulation reported sustained improvements in overall quality of life.<sup>35</sup> At 2 years of treatment, there were clinically meaningful improvements in overall quality of life (QoL) in 41% of subjects, with only 16% reporting declines. There were also significant improvements in epilepsy targeted and cognitive domains of QoL. The magnitude of improvement in QoL was less than that reported after mesial temporal lobectomy resulting in seizure remission but greater than that reported with continued medical

management.<sup>2,5,39,40</sup> Because the subjects with MTL in the RNS System trials were not considered candidates for temporal lobectomy, treatment with responsive MTL stimulation resulted in improvements in QoL that would not have otherwise been possible.

In conclusion, brain-responsive stimulation is a well-tolerated and reversible approach to treating MTL. Medically refractory patients with MTL have sustained reductions in the frequency of clinical seizures that reach 70%. The response is independent of past epilepsy treatments, and seizure reduction is achieved whether leads are placed within or close to the hippocampus. There are no stimulation-associated sustained AEs on mood or cognition, and some subjects experience memory improvement. Although responsive stimulation should be considered palliative, many subjects experience prolonged periods without seizures. Future clinical studies and additional experience with a variety of stimulation approaches should refine and further improve the response to treatment. The current clinical experience indicates that responsive stimulation offers a much-needed treatment option for patients with medically intractable MTL.

## ACKNOWLEDGMENTS

Baylor College of Medicine: Daniel Friedman, Ian L. Goldsmith, and Amit Verma. California Pacific Medical Center: Kenneth D. Laxer, and Peter B. Weber. Columbia University Medical Center: Hyunmi Choi, Derek J. Chong, Daniel Friedman, Steven C. Karceski, Guy M. McKhann, and Anil Mendiratta. Dartmouth-Hitchcock Medical Center: Joshua P. Aronson, Krzysztof A. Bujarski, Ann-Christine Duhaime, Gregory L. Holmes, Erik J. Kobylarz, Richard P. Morse, David W. Roberts, and Vijay M. Thadani. Emory University School of Medicine: Charles M. Epstein, Rebecca Fasano, Raymond E. Faught Jr, Suzette M. LaRoche, Page B. Pennell, and Andres A. Rodriguez Ruiz. Sandra L. Helmers, in memoriam. George Washington University School of Medicine and Health Sciences: Anthony J. Caputy, and Samuel J. Potolicchio Jr. Henry Ford Hospital: Ellen L. Air, David E. Burdette, Konstantin V. Elisevich, Shailaja Gaddam, Andrea Sneider Hakimi, Madhuri L. Koganti, Amit Ray, Jason M. Schwalb, Brien J. Smith, Marianna V. Spanaki-Varelas, and Vibhangini S. Wasade. Indiana University School of Medicine: Nicholas Barbaro, Omkar N. Markand, Meridith A. Runke, Dragos Sabau, Thomas C. Witt, and Robert M. Worth. Institute of Neurology and Neurosurgery at Saint Barnabas: Orrin Devinsky, Werner K. Doyle, Mangala A. Nadkarni, and Peter P. Widdess-Walsh. Johns Hopkins University School of Medicine: William S. Anderson, George I. Jallo, Eric H. Kossoff, Frederick A. Lenz, and Eva Katharina Ritzl. Keck School of Medicine of USC: Rami G. Apelian, Vidya P. Hawkins, Neda Heidari, Laura A. Kalayjian, Reed L. Levine, Lynn C. Liu, Andrew D. Ly, Johnson L. Moon, Jason S. Muir, George Nune, Ron A. Shatzmiller, Parastou Shilian, and Steven N. Sykes. Massachusetts General Hospital: Emad N. Eskandar, and Daniel B. Hoch. Mayo Clinic–Jacksonville, Florida: David R. Chabolla, Kent C. New, and Jerry J. Shih. Mayo Clinic–Rochester, Minnesota: Jeffrey W. Britton, and Gregory D. Cascino. Mayo Clinic–Scottsdale, Arizona: Joseph F. Drazkowski, Naresh P. Patel, and Joseph I. Sirven. Medical College of Georgia at Augusta University: Cole A. Giller, Ki Hyeon Lee, Mark R. Lee, Jeffrey M. Politsky, Joseph R. Smith, Suzanne M. Strickland, and Jeffrey A. Switzer. Medical University of South Carolina: Jimmy E. Couch, Steven Glazier, Jonathan J. Halford, Justin M. Nolte, Holly J. Skinner, Mimi Sohn, and William A. Vandergrift. Oregon Health & Science University: James J. Cereghino, Lia Ernst, Felicia A. Ferguson, Mary M. Ransom, Martin C. Salinsky, and William Brewster Smith. Rush University Medical Center: Donna C. Bergen, Richard W. Byrne, and Marvin A. Rossi. Swedish Medical Center: Lisa M. Caylor, Michael J. Doherty, and John D. Morgan.

The Cleveland Clinic Foundation: Andreas V. Alexopoulos, William E. Bingaman, Balu Krishnan, and Imad Michel Najm. Thomas Jefferson University Hospital: James J. Evans, Scott E. Mintzer, Maromi Nei, Ashwini D. Sharan, Michael R. Sperling, and Andro Zangaladze. University of Florida Medical Center: Jeffrey M. Chung, Jean E. Cibula, George A. Ghacibeh, and Steven N. Roper. University of Rochester Medical Center: Giuseppe Erba, Robert A. Gross, John Craig Henry, Charles Y. Liu, Webster H. Pilcher, Jason M. Schwalb, Olga Selioutski, and Thomas Wychowski. University of Texas Southwestern Medical Center: Mark A. Agostini, Sachin Dave, Ramon Diaz-Arrastia, Puneet K. Gupta, Ryan Hays, Bradley Lega, Christopher J. Madden, Pradeep N. Modur, and Louis Anthony Whitworth. University of Virginia School of Medicine: William J. Elias, and Mark S. Quigg. University of Wisconsin Hospital and Clinics: Azam S. Ahmed, Mustafa K. Baskaya, Brad R. Beinlich, John C. Jones, Lincoln F. Ramirez, Karl A. Sillay, and Evelyn C. Tunnell. Via Christi Epilepsy Center: Kore K. Liow, Andrew D. Massey, and Nazih Moufarrrij. Weill Cornell Medical College: Theodore H. Schwartz. Yale University School of Medicine: Pue Farooque, Evan J. Fertig, Jason L. Gerrard, Alexander M. Papanastassiou, Dennis D. Spencer, and Kenneth P. Vives. Sandra L. Helmers, and Susan S. Spencer, in memoriam.

## DISCLOSURE OF CONFLICT OF INTEREST

Author Eric B. Geller, has received support from, and/or has served as a paid consultant for NeuroPace for the RNS System Pivotal trial and as a speaker. Author Tara L. Skarpaas, has received support from, and/or has served as a paid consultant for NeuroPace, including employment and equity ownership/stock options. Author Robert E. Gross, has received research support from, and served as a paid consultant to NeuroPace, Inc., and Medtronic, Inc. NeuroPace, Inc., develops products related to the research described in this paper. The terms of these arrangements have been reviewed and approved by Emory University in accordance with its conflict of interest policies. Author Robert R. Goodman, has received support from, and/or has served as a paid consultant for NeuroPace. Author Gregory L. Barkley, has received support from the National Institutes of Health for the NIH MONEAD study of outcome of children born to women with epilepsy, and the American Academy of Neurology for time spent at meetings of the AMA-RBRVS Update Committee (RUC). Author Carl W. Bazil, has received support from, and/or has served as a paid consultant for Cipla. Author Michel J. Berg, has received support from Upsher-Smith Laboratories, Sunovion, NeuroPace, Lundbeck, Pfizer, King Pharmaceuticals, Sage Therapeutics, and Acorda Therapeutics for industry-sponsored research and is the principal investigator on a study sponsored by the U.S. Food and Drug Administration (FDA; contract HHSF223201110112A), a grant from the Epilepsy Foundation, and a gift from the American Epilepsy Society. Author Gregory Bergey, has received support from *Neurotherapeutics* in the capacity of Associate Editor. Author Andrew J. Cole, has received support from, and/or has served as a paid consultant for NeuroPace, Sage Therapeutics, and BrainVital/Precisis. Author Nathan B. Fountain, has received support from NeuroPace, Medtronic, UCB, and SK Life Sciences from research grants awarded to these companies. Author Ryder P. Gwinn, has received support from, and/or has served as a paid consultant for Medtronic and NeuroPace, although not during his participation in the RNS System Feasibility or Pivotal trials. Author Aamr A. Herekar, has received support from Sunovion, Eisai, and UCB for serving on their speaker's bureau. Author Lawrence J. Hirsch, has received support (honoraria) from NeuroPace for speaking via webinar. Author Kimford J. Meador, has received support from the National Institutes of Health and Sunovion Pharmaceuticals for research. The Epilepsy Study Consortium pays Dr. Meador's university for his research consultant time related to Eisai, GW Pharmaceuticals, NeuroPace, Novartis, Supernus, Turing Pharmaceuticals, Upsher-Smith Laboratories, UCB Pharma, and Vivus Pharmaceuticals. Author Eli M. Mizrahi, has received support from NeuroPace, the US Department of Defense, and royalties from McGraw-Hill Medical, Demos Medical Publishing, UpToDate, and Wolters Kluwer Publishers. Author Paul Rutecki, has received support from Veteran Affairs Research and Development and CURE for research. Author Christopher Skidmore, has received support from, and/or has served as a paid consultant for NeuroPace. Author David C. Spencer, has received support from, and/or has served as a paid consultant for NeuroPace. Author Paul C. Van Ness, has

received support from NeuroPace during the RNS System Pivotal trial. Author David G. Vossler, receives support from Acorda, Eisai, Marinus, Pfizer, SK Life Science, and UCB Pharmaceuticals for conducting clinical trials and is on the speaker's bureau and/or advisory boards for Eisai, Lundbeck, Sunovion, and UCB Pharmaceuticals. Author Gregory A. Worrell, has received support from the National Institutes of Health and Medtronic. Author Richard S. Zimmerman, has received support from, and/or has served as a paid consultant for NeuroPace. Author Kathy Cicora has received support from, and/or has served as a paid consultant for NeuroPace, including employment and equity ownership/stock options. Author Felice T. Sun, has received support from, and/or has served as a paid consultant for NeuroPace, including employment and equity ownership/stock options. Author Martha J. Morrell, has received support from, and/or has served as a paid consultant for NeuroPace, including employment and equity ownership/stock options. The remaining authors have no conflicts of interest that are relevant to this research activity. 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.

## REFERENCES

- Dredla BK, Lucas JA, Wharen RE, et al. Neurocognitive outcome following stereotactic laser ablation in two patients with MRI-/PET+mTLE. *Epilepsy Behav* 2016;56:44–47.
- Engel J Jr, McDermott MP, Wiebe S, et al. Early surgical therapy for drug-resistant temporal lobe epilepsy: a randomized trial. *JAMA* 2012;307:922–930.
- Kang JY, Wu C, Tracy J, et al. Laser interstitial thermal therapy for medically intractable mesial temporal lobe epilepsy. *Epilepsia* 2016;57:325–334.
- Pruitt R, Gamble A, Black K, et al. Complication avoidance in laser interstitial thermal therapy: lessons learned. *J Neurosurg* 2016;1–8.
- Wiebe S, Blume WT, Girvin JP, et al. A randomized, controlled trial of surgery for temporal-lobe epilepsy. *N Engl J Med* 2001;345:311–318.
- 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.
- 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.
- Morrell MJ. Responsive cortical stimulation for the treatment of medically intractable partial epilepsy. *Neurology* 2011;77:1295–1304.
- Zeger SL, Liang KY. Longitudinal data analysis for discrete and continuous outcomes. *Biometrics* 1986;42:121–130.
- Boex C, Seeck M, Vulliemoz S, et al. Chronic deep brain stimulation in mesial temporal lobe epilepsy. *Seizure* 2011;20:485–490.
- Bondallaz P, Boex C, Rossetti AO, et al. Electrode location and clinical outcome in hippocampal electrical stimulation for mesial temporal lobe epilepsy. *Seizure* 2013;22:390–395.
- Boon P, Vonck K, De HV, et al. Deep brain stimulation in patients with refractory temporal lobe epilepsy. *Epilepsia* 2007; 48:1551–1560.
- Cukiert A, Cukiert CM, Burattini JA, et al. Seizure outcome after hippocampal deep brain stimulation in a prospective cohort of patients with refractory temporal lobe epilepsy. *Seizure* 2014;23:6–9.
- McLachlan RS, Pigott S, Tellez-Zenteno JF, et al. Bilateral hippocampal stimulation for intractable temporal lobe epilepsy: impact on seizures and memory. *Epilepsia* 2010;51:304–307.
- Osorio I, Frei MG, Sunderam S, et al. Automated seizure abatement in humans using electrical stimulation. *Ann Neurol* 2005;57:258–268.
- Tellez-Zenteno JF, McLachlan RS, Parrent A, et al. Hippocampal electrical stimulation in mesial temporal lobe epilepsy. *Neurology* 2006;66:1490–1494.
- Velasco AL, Velasco M, Velasco F, et al. Subacute and chronic electrical stimulation of the hippocampus on intractable temporal lobe seizures: preliminary report. *Arch Med Res* 2000;31:316–328.
- Velasco AL, Velasco F, Velasco M, et al. Electrical stimulation of the hippocampal epileptic foci for seizure control: a double-blind, long-term follow-up study. *Epilepsia* 2007;48:1895–1903.
- Velasco M, Velasco F, Velasco AL, et al. Subacute electrical stimulation of the hippocampus blocks intractable temporal lobe seizures and paroxysmal EEG activities. *Epilepsia* 2000;41:158–169.
- Vonck K, Boon P, Achten E, et al. Long-term amygdalohippocampal stimulation for refractory temporal lobe epilepsy. *Ann Neurol* 2002;52:556–565.
- Engel J Jr, 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.
- Gross RE, Mahmoudi B, Riley JP. Less is more: novel less-invasive surgical techniques for mesial temporal lobe epilepsy that minimize cognitive impairment. *Curr Opin Neurol* 2015;28:182–191.
- Bien CG, Kurthen M, Baron K, et al. Long-term seizure outcome and antiepileptic drug treatment in surgically treated temporal lobe epilepsy patients: a controlled study. *Epilepsia* 2001;42:1416–1421.
- King-Stephens D, Mirro E, Weber PB, et al. Lateralization of mesial temporal lobe epilepsy with chronic ambulatory electrocorticography. *Epilepsia* 2015;56:959–967.
- Vonck K, Sprengers M, Carrette E, et al. A decade of experience with deep brain stimulation for patients with refractory medial temporal lobe epilepsy. *Int J Neural Syst* 2013;23:1250034.
- DiLorenzo DJ, Mangubat EZ, Rossi MA, et al. Chronic unlimited recording electrocorticography-guided resective epilepsy surgery: technology-enabled enhanced fidelity in seizure focus localization with improved surgical efficacy. *J Neurosurg* 2014;120:1402–1414.
- Enatsu R, Alexopoulos A, Bingaman W, et al. Complementary effect of surgical resection and responsive brain stimulation in the treatment of bitemporal lobe epilepsy: a case report. *Epilepsy Behav* 2012;24:513–516.
- 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.
- Spencer SS, Spencer DD, Williamson PD, et al. Combined depth and subdural electrode investigation in uncontrolled epilepsy. *Neurology* 1990;40:74–79.
- 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.
- Behrens E, Schramm J, Zentner J, et al. Surgical and neurological complications in a series of 708 epilepsy surgery procedures. *Neurosurgery* 1997;41:1–9.
- 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.
- Fisher R, Salanova V, Witt T, et al. Electrical stimulation of the anterior nucleus of thalamus for treatment of refractory epilepsy. *Epilepsia* 2010;51:899–908.
- 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.
- 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.
- Loring DW, Kapur R, Meador KJ, et al. Differential neuropsychological outcomes following targeted responsive neurostimulation for partial-onset epilepsy. *Epilepsia* 2015;56:1836–1844.
- Hermann BP, Seidenberg M, Dow C, et al. Cognitive prognosis in chronic temporal lobe epilepsy. *Ann Neurol* 2006;60:80–87.
- Sherman EM, Wiebe S, Fay-McClymont TB, et al. Neuropsychological outcomes after epilepsy surgery: systematic review and pooled estimates. *Epilepsia* 2011;52:857–869.
- Markand ON, Salanova V, Whelihan E, et al. Health-related quality of life outcome in medically refractory epilepsy treated with anterior temporal lobectomy. *Epilepsia* 2000;41:749–759.
- Spencer SS, Berg AT, Vickrey BG, et al. Health-related quality of life over time since resective epilepsy surgery. *Ann Neurol* 2007;62:327–334.