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Neurology 2011;77;1295; Published online before print September 14, 2011;
DOI 10.1212/WNL.0b013e3182302056

This information is current as of June 13, 2012

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AMERICAN ACADEMY OF NEUROLOGY®

Responsive cortical stimulation for the treatment of medically intractable partial epilepsy

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ABSTRACT

Objectives: This multicenter, double-blind, randomized controlled trial assessed the safety and effectiveness of responsive cortical stimulation as an adjunctive therapy for partial onset seizures in adults with medically refractory epilepsy.

Methods: A total of 191 adults with medically intractable partial epilepsy were implanted with a responsive neurostimulator connected to depth or subdural leads placed at 1 or 2 predetermined seizure foci. The neurostimulator was programmed to detect abnormal electrocorticographic activity. One month after implantation, subjects were randomized 1:1 to receive stimulation in response to detections (treatment) or to receive no stimulation (sham). Efficacy and safety were assessed over a 12-week blinded period and a subsequent 84-week open-label period during which all subjects received responsive stimulation.

Results: Seizures were significantly reduced in the treatment (−37.9%, n = 97) compared to the sham group (−17.3%, n = 94; $p = 0.012$) during the blinded period and there was no difference between the treatment and sham groups in adverse events. During the open-label period, the seizure reduction was sustained in the treatment group and seizures were significantly reduced in the sham group when stimulation began. There were significant improvements in overall quality of life ($p < 0.02$) and no deterioration in mood or neuropsychological function.

Conclusions: Responsive cortical stimulation reduces the frequency of disabling partial seizures, is associated with improvements in quality of life, and is well-tolerated with no mood or cognitive effects. Responsive stimulation may provide another adjunctive treatment option for adults with medically intractable partial seizures.

Classification of evidence: This study provides Class I evidence that responsive cortical stimulation is effective in significantly reducing seizure frequency for 12 weeks in adults who have failed 2 or more antiepileptic medication trials, 3 or more seizures per month, and 1 or 2 seizure foci. ***Neurology*® 2011; 77:1295–1304**

GLOSSARY

AE = adverse event; **AED** = antiepileptic drug; **BDI-II** = Beck Depression Inventory; **BEP** = blinded evaluation period; **CES-D** = Center for Epidemiologic Studies Depression Scale; **DBS** = deep brain stimulation; **GEE** = generalized estimating equation; **PD** = Parkinson disease; **QOLIE-89** = Quality of Life in Epilepsy inventory; **SAE** = serious AE; **SUDEP** = sudden unexplained death in epilepsy.

Despite antiepileptic drugs (AEDs), more than 30% of persons with epilepsy continue to have seizures.[1] Many are not candidates for epilepsy surgery. Direct brain stimulation may provide a nondestructive treatment option for some persons with medically intractable partial seizures. Deep brain stimulation (DBS) is a Food and Drug Administration–approved treatment for Parkinson disease (PD) and essential tremor[2] and has recently been investigated as a treatment for epilepsy.[3] One potential approach to treating epilepsy is to provide stimulation directly to the seizure focus in response to epileptiform electrographic events. This report presents the results of the first controlled trial of responsive cortical stimulation in adults with medically intractable partial onset seizures.

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Patient Page

From NeuroPace, Inc., Mountain View, CA.

Study funding: Sponsored by NeuroPace, Inc., which participated in acquisition of data, statistical analysis, study supervision, and approval of data.
Disclosure: Author disclosures are provided at the end of the article.

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METHODS Subjects were 18–70 years of age, had partial onset seizures that had not been controlled with ≥2 trials of AEDs, had ≥3 disabling seizures per month on average, and had undergone standard diagnostic testing that localized 1 or 2 epileptogenic regions.

The study protocol was approved by the institutional review boards of all participating investigation sites. All patients gave written informed consent. The study was registered on www.clinicaltrials.gov (NCT00264810).

The RNS® System (NeuroPace, Mountain View, CA) provides responsive cortical stimulation via a cranially implanted programmable neurostimulator connected to 1 or 2 recording and stimulating depth or subdural cortical strip leads that are surgically placed in the brain according to the seizure focus. The neurostimulator continually senses electrocorticographic activity and is programmed by the physician to detect abnormal electrocorticographic activity and then provide stimulation. The physician adjusts detection and stimulation parameters for each patient to optimize control of seizures.

The RNS System Pivotal trial is a randomized, double-blind, multicenter, sham-stimulation controlled study. The study design and subject flow is illustrated in figure 1.

AEDs were to be held constant through the blinded evaluation period (BEP), and then could be adjusted as needed. Benzodiazepines for seizure clusters or prolonged seizures were permitted.

Subjects recorded seizures daily. Disabling seizures were simple partial motor, complex partial, and secondarily generalized tonic-clonic seizures. The Quality of Life in Epilepsy (QOLIE-89) inventory,[4] neuropsychological testing and mood inventories including the Beck Depression Inventory (BDI-II),[5] and the Center for Epidemiologic Studies Depression Scale (CES-D)[6] were obtained before implantation, at the end of the BEP, and at 1 and 2 years after implantation.

Adverse events (AEs) were classified by the investigator as serious or mild, and as device-related (includes device relation uncertain) or not device-related, then coded according to the MedDRA coding system. An independent Data Monitoring Committee reviewed all AEs. A second committee determined whether deaths met criteria for sudden unexplained death in epilepsy (SUDEP).

Subjects were assigned 1:1 to treatment or sham groups using an adaptive randomization algorithm controlling for investigational site, location and number of seizure onsets, and prior epilepsy surgery. A blinded physician gathered all outcome data and a nonblinded physician managed the neurostimulator. To maintain the subject blind, all subjects underwent actual or sham programming of the neurostimulator to ensure that time with the physician was similar. The blind was to be maintained until all subjects completed the trial.

The prespecified primary effectiveness endpoint was the difference between the treatment and sham groups in the reduction of mean seizure frequency during the BEP relative to the preimplant period, defined as the 12 weeks of the baseline period that concluded with the subject's eligibility for implantation. The primary endpoint variable was the group-by-time interaction term in a generalized estimating equation (GEE) model, where group refers to therapy allocation (treatment or sham), time refers to the trial period (preimplant or BEP), and the dependent variable is seizure frequency. A significant group-by-time interaction term demonstrates a significantly greater reduction in seizure frequency in the treatment group than the sham group during the BEP compared to the preimplant period.

The prespecified primary safety objective was to establish that the serious AE (SAE) rate was no worse than the literature-derived SAE rate for comparable procedures. Secondary safety endpoints were the percentage of subjects reporting AEs and the types of AEs for the treatment and sham groups during the BEP (Fisher exact test), changes in neuropsychological functioning and mood inventories relative to baseline (paired t test) and differences between groups (2-sample t test).

RESULTS A total of 240 individuals enrolled at 32 US centers from December 2005 to November 2008, and 191 were implanted with the neurostimulator and leads at 31 centers. Demographics and baseline characteristics for implanted subjects are summarized in table 1.

The blind was successfully maintained (blinding index = 0.572[7]). At the end of the BEP, 24% said that they did not know to which group they had been randomized, 33% guessed incorrectly, and 43% guessed correctly.

Mean seizure frequency was significantly reduced in the treatment compared to the sham group (p = 0.012), as presented in table 2. In the first postimplant month (before randomization), there was a reduction in mean seizure frequency in both subject groups (figure 2). However, the implant-associated seizure reduction in the sham group abated in subsequent months. The difference in seizure frequency between the treatment and sham groups increased over time from implant and was greatest during the final month of the BEP, when the sham group approached their preimplant seizure frequency.

The results of the primary analysis were robust. Statistical significance remained when the primary analysis was repeated excluding the 6 subjects with changes in AEDs before the end of the BEP, when the subject with the most extreme seizure frequency values was excluded and when the analysis was adjusted for investigational site. Inclusion of interaction terms in the GEE model demonstrated that the treatment response did not depend on whether seizures arose from the mesial temporal lobe vs other brain regions, whether there were 1 or 2 seizure foci, or whether the subjects had been previously treated with an epilepsy surgery or vagus nerve stimulation.

Additional efficacy analyses showed favorable changes in the treatment group and sham groups during the BEP. The responder rate over the BEP (percentage of subjects with a ≥50% reduction in seizures) was 29% in the treatment group and 27% in the sham group. Two subjects (2.1%) in the treatment group (and none in the sham group) were seizure-free during the 12-week BEP. Although both the treatment and sham groups experienced more seizure-free days over the first month of the BEP relative to baseline, seizure-free days continued to in-

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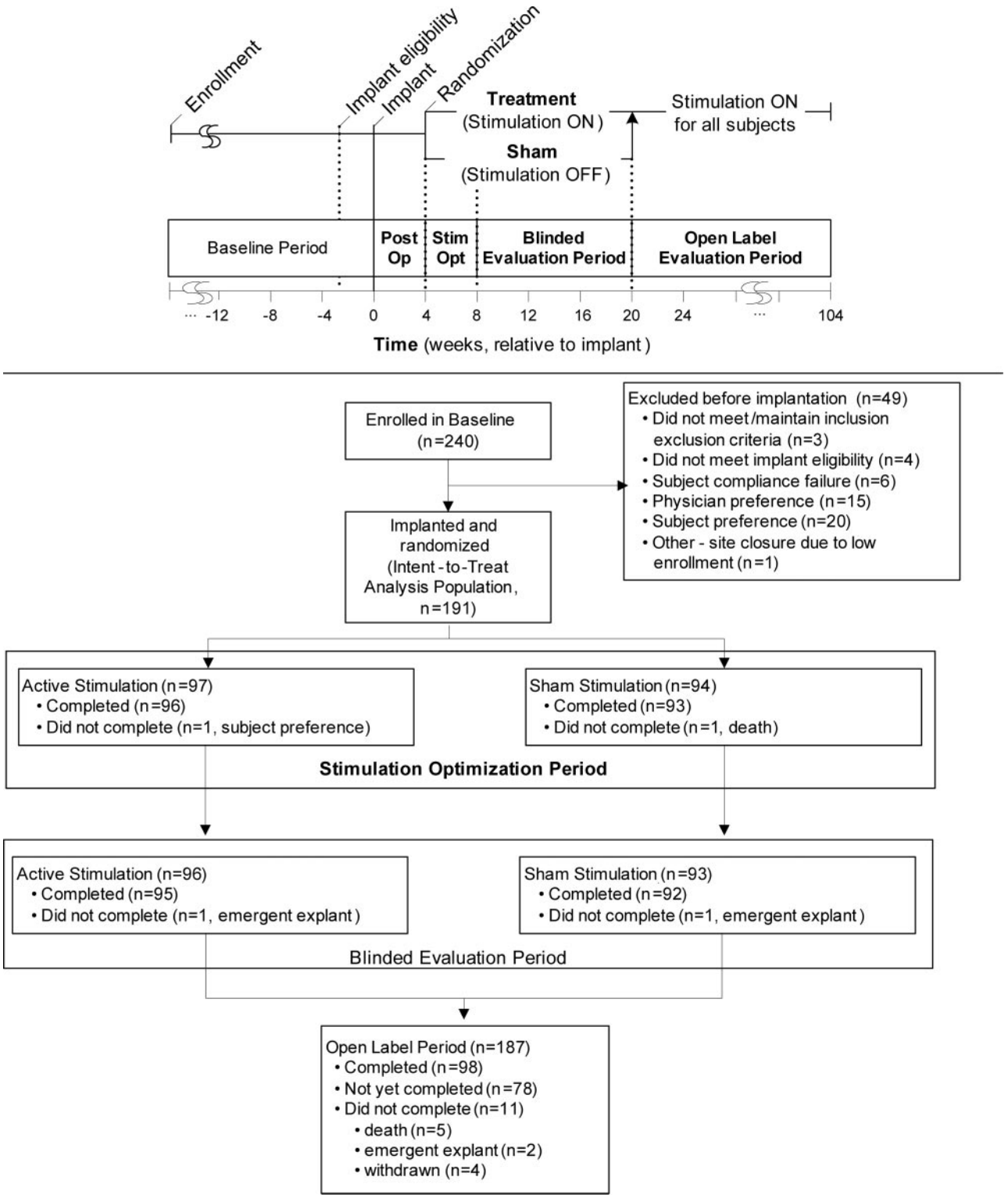
Figure 1 Trial design and subject flow



Subjects meeting criteria for implantation had adequate seizure counts and maintained stable antiepileptic drug regimens over 12 weeks within the baseline period. After implantation, the neurostimulator was programmed to sense and record the electrocorticogram, but not to deliver stimulation (4-week postoperative stabilization period). Subjects were then randomized 1:1 to the treatment group or to the sham stimulation group. Only neurostimulators for subjects in the treatment group were programmed to deliver stimulation (4-week stimulation optimization period). The treatment group continued to receive responsive stimulation and the sham group did not over the 12-week blinded evaluation period (BEP). After the BEP (20 weeks postimplant), all subjects were able to receive responsive stimulation over an 84-week open label period (OLP). At the time of the data cutoff (June 4, 2010), all subjects had completed the BEP and 1 year postimplant; the second year of the OLP was ongoing. In subjects in the treatment group and all subjects in the OLP, stimulation was enabled 99% of the time.

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Table 1 Demographic data and baseline characteristics of implanted subjects

Characteristics	All implanted (n = 191)	By randomization group		p Value[a]
		Treatment (n = 97)	Sham (n = 94)	
Sex, % female	48	48	47	0.820
Mean ± SD age, y (range)	34.9 ± 11.6 (18–66)	34.0 ± 11.5 (18–60)	35.9 ± 11.6 (18–66)	0.239
Mean ± SD years with epilepsy (range)	20.5 ± 11.6 (2–57)	20.0 ± 11.2 (2–57)	21.0 ± 12.2 (2–54)	0.546
Mean ± SD no. of AEDs at enrollment (range)	2.8 ± 1.2 (0–8)	2.8 ± 1.3 (1–8)	2.8 ± 1.1 (0–6)	0.926
Mean ± SD no. baseline seizures per day (range)	1.2 ± 2.2 (0.1–12.1)	1.2 ± 2.0 (0.1–10.5)	1.2 ± 2.4 (0.1–12.1)	0.875
Mesial temporal seizure onset (vs other), %	50	49	50	0.943
Two seizure foci (vs one), %	55	49	62	0.089
Prior therapeutic surgery for epilepsy, %	32	35	30	0.437
Prior intracranial EEG monitoring, %	59	65	53	0.098
Prior VNS, %	34	31	36	0.443

Abbreviations: AED = antiepileptic drug; VNS = vagus nerve stimulation.
[a] p Value for across-group comparisons (treatment compared to sham) using 2-sample t test and χ^2 (for proportions).

crease in the treatment group but declined for the sham group. By the third month of the BEP, the treatment group had 27% fewer days with seizures whereas the sham group experienced 16% fewer days (change in proportion of seizure-free days, $p = 0.048$, paired t test).

Subjects in the sham group had a statistically significant reduction in mean seizure frequency compared to the preimplant period when responsive stimulation began in the OLP ($p = 0.04$ paired t test, figure 2). Across all subjects, the seizure reduction was sustained, and even improved, over time. The responder rate at 1 year postimplant was 43% (n = 177) and for those subjects who had reached 2 years postimplant was 46% (n = 102). As of the data cutoff date, 13 subjects (7.1%) were seizure-free over the most recent 3-month period.

QOLIE-89 overall t scores improved relative to baseline in both treatment and sham groups at the end of the BEP ($p = 0.040$ and $p = 0.032$; paired t test) and there were continued improvements for all subjects combined at 1 year ($p < 0.001$) and 2 years ($p = 0.016$) as well as in primary scale t scores for language ($p < 0.001$ and $p = 0.025$), memory ($p < 0.001$ and $p = 0.004$), attention/concentration ($p < 0.001$ and $p = 0.019$), work/driving/social function ($p = 0.001$ and $p = 0.002$), and health discouragement and seizure worry (all $p < 0.001$ both time points).

The primary safety endpoint was achieved. The SAE rate for the RNS System over the first 28 days (device related and not device related) was 12%, which is not worse than the prespecified literature-derived comparator of 15% for implantation of intracranial electrodes for seizure localization and epilepsy surgery.[8–12] The

Table 2 Mean % change in seizure frequency during the blinded evaluation period, intent-to-treat population

Blinded evaluation period	Mean % change from preimplant period (GEE)[a] (95% confidence interval)		p Value[b]
	Treatment (n = 97)	Sham (n = 94)	
Entire BEP (n = 191)	−37.9% (−46.7%, −27.7%)	−17.3% (−29.9%, −2.3%)	0.012
Month 1 (3rd month postop)	−34.2% (−44.1%, −22.6%)	−25.2% (−37.1%, −11.1%)	0.279
Month 2 (4th month postop)	−38.1% (−47.3%, −27.3%)	−17.2% (−30.5%, −1.3%)	0.016
Month 3 (5th month postop)	−41.5% (−52.0%, −28.7%)	−9.4% (−29.5%, 16.4%)	0.008

Abbreviations: BEP = blinded evaluation period; GEE = generalized estimating equation.
[a] The GEE model estimates seizure frequency on the logarithmic scale, accounting for onset zone, number of seizure foci, and prior resection.
[b] p Values of the group-by-time interaction parameters in the GEE model where the group-by-time interaction estimates the difference in seizure frequency reduction between the treatment and sham groups during the BEP compared to the preimplant period.

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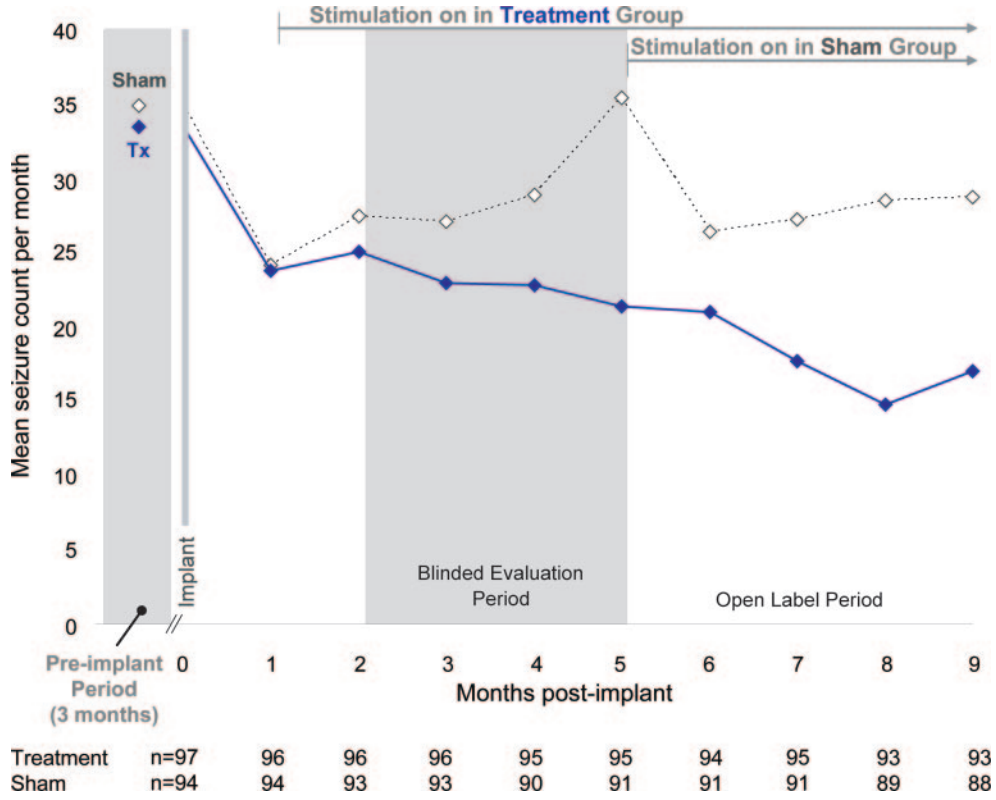
Figure 2 Mean disabling seizures by month, observed data



N represents the number of subjects with seizure data during that interval. Randomization occurs at 1 month postimplant. The treatment group begins to receive responsive stimulation during the stimulation optimization period and continues to receive responsive stimulation through the blinded evaluation period (BEP). The sham group does not receive responsive stimulation until after the BEP.

SAE rate for the RNS System during the implant and first 84 days (device related and not device related) was 18.3%, which is not worse than the prespecified literature-derived comparator of 36% for implantation and treatment with DBS for PD.[13–17]

There was no difference between the treatment and sham groups in the percentage of subjects with mild or serious AEs (overall or for any type) over the BEP. Two subjects had device-related SAEs during the BEP; one subject (treatment) had one event related to a change in seizures and one subject (sham) had 3 events related to a change in seizures.

All device-related AEs (serious and mild) occurring through 1 year postimplant in 2.5% or more of the subjects are presented by study period in table 3.

AEs of special relevance to persons with epilepsy with an implanted device were considered over the entire 340 years of patient experience.

The overall rate of intracranial hemorrhage was 4.7% (9/191 subjects). Six of the 9 events were postoperative: 3 surgically evacuated epidural hematomas, 2 intraparenchymal hemorrhages that resolved without surgery, and 1 subdural hematoma. The other 3 events were subdural hematomas attributed to seizure-related head trauma. Two of the 9 events were considered mild AEs. Therefore, 2.1% of subjects had a serious hemorrhage not due to seizure-related head trauma. There were no permanent neurologic sequelae from any hemorrhage.

SAEs related to implant or incision site infection occurred in 5.2% of subjects (10/191) and devices were explanted in 4 of these subjects. Five subjects had infections that began after the postoperative period: 2 were attributed to secondarily infected scalp lacerations from a seizure. All infections involved soft tissue only; there were no infections of the brain or skull.

Six subjects died: 1 from lymphoma, 1 subject with a history of depression committed suicide, and 4 subject deaths were attributed to SUDEP (3 had stimulation enabled).

Preimplant neuropsychological assessments indicated that 52.7% of the implanted subjects had verbal memory dysfunction and 56.2% had visuospatial memory dysfunction (score $\leq$ fifth percentile per age-based normative data for the Rey Auditory Verbal Learning Test I–V and Brief Visuospatial Memory Test–Revised, total recall). During the BEP, there was no difference between the treatment and sham groups in the frequency of cognitive AEs, in-

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Table 3 Device-related[a] mild and serious AEs in ≥2.5% of subjects by study period through 1 year

	Postop (implant–week 4)	Stimulation optimization (weeks 4–8)	Blinded evaluation (weeks 8–12)	Open label, year 1 (weeks 20–52)	All study periods through 1 year[b]
No. of subjects entering (N)/total implant years within interval	191/14.7	191/14.6	189/43.0	187/113.2	191/185.5
MedDRA preferred term, % subjects[c] (no. subjects)					
Implant site pain	9.9 (19)	2.1 (4)	0.5 (1)	3.7 (7)	15.7 (30)
Headache	2.6 (5)	3.1 (6)	2.6 (5)	5.3 (10)	10.5 (20)
Procedural headache	8.9 (17)	—	—	0.5 (1)	9.4 (18)
Dysesthesia	—	1.0 (2)	2.1 (4)	3.7 (7)	6.3 (12)
Simple partial seizures (sensory)	1.0 (2)	1.0 (2)	1.1 (2)	3.2 (6)	6.3 (12)
Complex partial seizures	0.5 (1)	0.5 (1)	1.1 (2)	4.3 (8)	5.8 (11)
Complex partial seizures increased	—	—	2.1 (4)	4.3 (8)	5.8 (11)
Photopsia	—	1.0 (2)	—	3.7 (7)	4.7 (9)
Tonic-clonic seizures increased	—	0.5 (1)	0.5 (1)	4.3 (8)	4.7 (9)
Implant site swelling	3.7 (7)	0.5 (1)	—	—	4.2 (8)
Memory impairment	1.0 (2)	0.5 (1)	0.5 (1)	2.1 (4)	4.2 (8)
Device interaction	1.6 (3)	0.5 (1)	0.5 (1)	1.1 (2)	3.7 (7)
Tonic-clonic seizures exacerbated	—	0.5 (1)	—	3.2 (6)	3.7 (7)
Complex partial seizures exacerbated	—	—	1.1 (2)	2.1 (4)	3.1 (6)
Depression	—	0.5 (1)	1.1 (2)	1.6 (3)	3.1 (6)
Implant site infection	2.6 (5)	—	—	1.1 (2)	3.1 (6)
Muscle twitching	1.0 (2)	1.0 (2)	0.5 (1)	0.5 (1)	3.1 (6)
Device lead damage	—	—	—	2.7 (5)	2.6 (5)
Dizziness	1.0 (2)	1.0 (2)	—	0.5 (1)	2.6 (5)
Paraesthesia	1.0 (2)	—	0.5 (1)	1.1 (2)	2.6 (5)
Simple partial seizures (motor)	1.0 (2)	0.5 (1)	1.1 (2)	0.5 (1)	2.6 (5)

Abbreviation: AE = adverse event.
[a] Includes AEs classified as device relation uncertain.
[b] Row totals may not sum to totals in this column because some subjects may have had AEs in more than one period.
[c] % Subjects = no. subjects with event/no. of subjects entering interval.

cluding memory. There was no deterioration in any neuropsychological measure at the end of the BEP or at 1 or 2 years after implantation. In fact, there were statistically significant group improvements at 1 and 2 years in aspects of verbal functioning, visuospatial ability, and memory ($p < 0.05$).

Many subjects entered the trial with a history of depression (49.7%) or suicidality (5.2%). Before implant, 42.0% met criteria for depression (BDI-II or CES-D) and 10.2% endorsed passive suicidality (BDI-II). There were no adverse changes in the mood inventories at the end of the BEP or at 1 or 2 years after implant.

There was no difference in the percentage of subjects in the treatment and sham groups experiencing an AE related to depression or suicidality during the BEP. Over the entire study, 13.6% of subjects had AEs related to depression (all mild); 16 of these 26 subjects had a history of depression and one had recently lost a loved one. AEs related to suicidality were reported in 6.8% of subjects,[13] including 6 subjects (3.1%) with SAEs. All had a history of depression or anxiety, or met criteria for depression on the BDI-II or CES-D. One of the 13 subjects committed suicide 4 weeks after stimulation was enabled in the OLP, after a long-distance move and during an intercurrent depression.

DISCUSSION Responsive cortical stimulation significantly reduced the frequency of disabling seizures in adults with partial seizures who had failed multiple other epilepsy treatments. During a 12-week blinded period, the group receiving stimulation experienced a statistically significant reduction in seizures compared to a group receiving sham stimulation and the seizure reduction was sustained and even improved when all subjects received stimulation in an open-label period.

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As anticipated, there was an initial reduction in seizures after the implantation procedure. The effect of neurosurgical procedures on seizure frequency has been previously described[18–20] and is unlikely to be related to a microlesion effect. A reduction in seizures of similar magnitude and duration occurred in a group randomized to sham stimulation in a blind, controlled trial of DBS for partial epilepsy[3] in which the target was the anterior thalamic nuclei, rather than the cortex as in the RNS System trial. Whether the implant effect is related to anesthesia or to the surgical procedure is not known; however, the effect is transient. In this trial, the implant effect in the sham group had largely resolved by the fifth month postimplant.

The favorable effect of stimulation independent of the implant effect was apparent in the still-blinded subjects in the sham group at the start of the open period. When responsive stimulation was first delivered, seizures were significantly reduced compared to the preimplant baseline. Also, the reduction in seizures was sustained in both subject groups throughout the open period. Nearly half of the subjects who had the opportunity to complete 2 years postimplant achieved a 50% or greater reduction in seizures. Given the long duration and severity of their epilepsy, and many treatment failures, this sustained seizure reduction with responsive stimulation is clinically meaningful.

The clinical meaningfulness of the treatment response is further supported by significant improvements in QOL at 1 and 2 years after treatment, including domains strongly associated with QOL such as social function, health concerns, and cognition.[21,22] Improvements in cognition are of special importance. In a survey conducted by the International Bureau for Epilepsy,[23] more than half of adults reported that cognitive impairment significantly affected their ability to engage in work, education, and leisure activities and had a negative impact on family and relationships. The overall improvement in QOL seen in the RNS System trial is especially meaningful when considering that the natural history of medically intractable epilepsy is of continued deterioration in QOL.[24]

The overall safety of the RNS System was favorable when compared to the risks of alternative treatments and comparable procedures and to the risks of frequent seizures. Anticipated risks of any neurosurgical procedure and implanted device include hemorrhage and infection. Hemorrhage occurs in 1.6% to 16% of persons implanted with intracranial leads for an epilepsy surgery evaluation[9–12,25,26] and in 3% to 4.5% treated with DBS for movement disorders[27] or epilepsy.[3] In the RNS System trial, serious intracranial hemorrhage not associated with seizure-related head trauma occurred in 2.1% of subjects over the 340 years of patient experience and none had persistent neurologic consequences.

Infection rates were also not higher than expected. The rate of infection is about 2% with acute implantation of intracranial leads,[8] 5% with epilepsy surgery[28] or DBS for movement disorders,[27] and 12.7% in a trial of DBS for epilepsy[3]; about half lead to explantation. Serious AEs in the RNS System trial due to nonseizure-related incision or implant site infection occurred in 4.2% of subjects; 4 of these 10 subjects were explanted. There were no permanent neurologic consequences.

The tolerability of responsive cortical stimulation can also be considered in the context of the anticipated adverse effects of AEDs. In one assessment of persons with epilepsy,[29] the overall mean number of AED-related adverse effects was 6.5, and AEs related to cognition and coordination were the strongest predictors of impaired QOL. The most common adverse effects in trials of the newer AEDs were dizziness, somnolence, headache, abnormal thinking or confusion, and nausea and vomiting.[30] In the RNS System trial there were no significant differences in any AE between the treatment and sham groups, and reports of cognitive, coordination, or gastrointestinal symptoms were rare.

The risks of an epilepsy treatment should also be considered in the context of the risks posed by frequent seizures, such as depression, suicidality, memory impairment, and SUDEP. Depression and suicidality are frequent comorbid conditions in adults with medically intractable partial seizures treated with AEDs.[31–38] Half of the subjects in the RNS System trial had a history of depression and more than 5% had a history of suicidality; a similar percentage met objective criteria for depression and suicidality before implant. Responsive cortical stimulation did not increase the risk for depression or suicidality.

Persons with medically intractable epilepsy are at risk for memory deterioration,[22] especially those with a long duration of seizures, high seizure frequency and severity, and temporal lobe seizures.[39] As expected based on the demographics, half of the subjects in the RNS System trial had preexisting memory difficulties. Responsive cortical stimulation did not adversely affect memory. In fact, there were improvements in some aspects of memory.

The rate of SUDEP with severe medically intractable epilepsy is estimated to be 9.3/1,000 patient-years.[40] There were 4 SUDEP deaths over the 340 patient-years, within the expected range. Patient-

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years are not sufficient to calculate a confident SUDEP rate.

The RNS System provides individualized treatment targeted to the seizure focus. As compared to continuous stimulation systems, the RNS System senses and records the patient's electrocorticographic activity, then provides stimulation in response to previously identified electrocorticographic pattern abnormalities. The physician reviews the response to stimulation on stored electrocorticograms, and then adjusts programming for each individual to achieve the best clinical response.

This multicenter, randomized, double-blind sham stimulation controlled trial provides Class I level of evidence that responsive cortical stimulation is effective in significantly reducing the frequency of disabling partial onset seizures that were intractable to AEDs, and in many cases, to vagus nerve stimulation or epilepsy surgery. Improvements in QOL overall and in domains related to health concerns, social functioning, and cognition support the clinical meaningfulness of the treatment response. Safety was acceptable compared to alternative and comparable procedures and to the risks of frequent seizures. Stimulation was well-tolerated and there were no adverse effects on cognition or mood. Given these findings, responsive cortical stimulation may provide another much-needed treatment option for persons with medically intractable partial seizures.

COINVESTIGATORS

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ACKNOWLEDGMENT

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DISCLOSURE

Dr. Morrell is an employee of and holds stock options in NeuroPace, Inc.; is an employee of Stanford University in epilepsy clinical practice (20% effort); has received speaker honoraria from GlaxoSmithKline; serves on the editorial board of *Neurostimulation*; is on the nominating committee of the American Society of Experimental Neurotherapeutics (ASENT); and is on the Board of Directors of the Epilepsy Research Foundation.

Received February 2, 2011. Accepted in final form May 24, 2011.

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Responsive cortical stimulation for the treatment of medically intractable partial epilepsy

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Neurology 2011;77;1295; Published online before print September 14, 2011;
DOI 10.1212/WNL.0b013e3182302056

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