



Responsive Cortical Stimulation: The 21% Solution?

Responsive Cortical Stimulation for the Treatment of Medically Intractable Partial Epilepsy.

Morrell MJ, RNS System in Epilepsy Study Group. *Neurology* 2011;27;77(13):1295–1304.

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.

Commentary

Despite decades of antiepileptic drug development and refinements in neurosurgical treatment, many patients continue to have uncontrolled, disabling epilepsy. New methods to stop seizures are needed, and this report by Morrell et al. represents genuine innovation, because it uses an entirely new method to treat pharmacoresistant focal seizures.

More than 50 years ago, Penfield and Jasper (1) showed that direct electrical stimulation of the cortex suppressed epileptiform discharges. It was later observed that afterdischarges elicited during cortical stimulation mapping could be aborted by restimulation at the same electrodes (2). In addition, cyclical, low-intensity, high-frequency electrical stimulation of the hippocampus with depth electrodes was found to produce long-term suppression of temporal lobe seizures (3, 4). Subsequent bedside studies during invasive monitoring demonstrated that software designed to detect spontaneous seizures could abort them by triggered direct electrical stimulation of the focus (5, 6). This was termed closed-loop stimulation, and it was postulated that successful termination

of seizures depended on how early in the course of the seizure the stimulation was delivered and the proximity of the stimulation site to the actual seizure focus (7).

This work led to development of an implantable, programmable system to use chronically for closed-loop stimulation for treatment of focal epilepsy. This device, the responsive neurostimulator (RNS), is implanted cranially and is connected to one or two chronically implanted intracranial depth or strip electrodes, each with up to four contacts (7). Seizure detection is performed by three different, configurable, detection algorithms, and stimulation is also adjustable in regards to frequency, amplitude, and the combination of electrodes to which it is delivered. Preliminary evidence of safety and efficacy of the device was obtained prior to the pivotal controlled trial (7).

The cohort of the current study had clinical characteristics similar to patients typically enrolled in trials of investigational antiepileptic medications or the vagal nerve stimulator, except for the additional requirement that they be judged to have one or two localizable sites of seizure origination that could be covered by the device's electrodes. The complication rate was similar to that reported for invasive epilepsy monitoring (8). Moderate and serious device-related adverse effects occurred in 2.5% of patients in the first year, and serious hemorrhage not caused by seizure-related head trauma occurred in 2.1%.



Incision site or implant infection occurred in 5.2% of patients, but no infections of the brain or skull were seen; however, explanting of the device was necessary in 2.1%. Although it is conceivable that patients might have symptoms when cortical stimulation was occurring, it was confirmed that they were not able to guess, beyond chance, to what group they had been randomly assigned.

It is notable that there was an overall approximately 30% reduction in seizure frequency in both the control and treated groups in the first month after RNS implantation before the time that treatment began, and this did not return to the pre-implantation seizure rate until the fifth postoperative month. It is not clear whether this represents a placebo effect, akin to what is observed in investigational antiepileptic medication trials, or a physiological effect of the surgery itself—transient or even persistent seizure reductions have been observed after invasive monitoring in the absence of resection (9). This drop in seizure frequency in the early postoperative months resulted in a 27% responder rate (a 50% or greater seizure reduction relative to the baseline frequency) in the *control* group and a 29% responder rate in the stimulated group during the 12-week blinded randomized period. During this period, 2.1% of the stimulated group became seizure free, but none of the control group did. The randomized period was followed by an unblinded open extension study, during which all patients received stimulation; the responder rate was 43% at the end of the first postoperative year.

The finding of a significant, approximately 21%, reduction in seizure frequency in stimulated patients (−37.9%) relative to controls (−17.3%) during the randomized evaluation period in this well-designed trial has led to submission of a premarket approval application to the FDA. If introduced into clinical practice, it is likely that device implantation would initially be offered to a very limited patient subgroup. The modest demonstrated efficacy in the clinical trial means that RNS is not an alternative to surgical resection. Also, it should only be considered after failure of numerous trials of antiepileptic drugs and vagal nerve stimulation, because the pivotal clinical trial does not provide evidence that it is more effective than these other treatments although it does demonstrate that it has a higher morbidity.

It should be recognized that this trial was designed to provide definitive evidence of RNS benefit, not to compare its efficacy to that of other treatments. Because of the paucity of studies that directly compare different epilepsy therapies, the rate of seizure reduction, or the responder rates in placebo controlled trials of different therapies are sometimes compared to estimate relative efficacy. This exercise may be somewhat misleading for RNS, however, because this is a complicated treatment. If this device is introduced into clinical practice, there are many factors that might affect outcomes.

Just as with epilepsy surgery, RNS requires precise delineation of the location and extent of the seizure onset zones. In patients for whom seizures originate from discrete zones involving essential language or motor cortex, RNS could be an appropriate alternative to the current surgical option, multiple subpial transections, which has unclear effectiveness (10). Patients with well-defined bilateral seizure onset zones—for example, those with bilateral temporal lobe epilepsy and

mesial temporal sclerosis—might also be considered for implantation. Patients who are determined to be poor resection candidates because of diffuse, multifocal, or ill-defined seizure origination would also be expected to respond poorly to RNS. More experience with neural stimulation might better define specific subgroups of patients with focal epilepsy who have a higher chance of responding to this modality.

This new epilepsy therapy also lends itself to additional innovation. Efficacy might be improved if new algorithms are developed to detect seizures earlier. Improved electrode arrays might more completely cover regions of seizure origination. If electrical stimulation still proved inadequate to arrest seizures completely, other interventions, such as release of neuroactive substances or rapid focal cooling, might be coupled to the seizures. RNS could just be the prototype of a new treatment paradigm.

This successful clinical trial of this complex intervention in a heterogeneous patient population at 32 centers is remarkable, even though the demonstrated seizure reduction is very modest. Hopefully, this achievement will break a barrier to development of different ways to treat epilepsy and will be the forerunner of many novel approaches to therapy.

by John W. Miller MD, PhD

References

1. Penfield W, Jasper H. Electroconvulsive therapy. In: *Epilepsy and the Functional Anatomy of the Human Brain*. Boston: Little, Brown, 1954:692–738.
2. Lesser RP, Kim SH, Beyderman L, Miglioretti DL, Webber WR, Bare M, Cysyk B, Krauss G, Gordon B. Brief bursts of pulse stimulation terminate afterdischarges caused by cortical stimulation. *Neurology* 1999;10;53:2073–2081.
3. Velasco M, Velasco F, Velasco AL, Boleaga B, Jimenez F, Brito F, Marquez I. Subacute electrical stimulation of the hippocampus blocks intractable temporal lobe seizures and paroxysmal EEG activities. *Epilepsia* 2000;41:158–169.
4. Velasco AL, Velasco F, Velasco M, Trejo D, Castro G, Carrillo-Ruiz JD. Electrical stimulation of the hippocampal epileptic foci for seizure control: A double-blind, long-term follow-up study. *Epilepsia* 2007;48:1895–1903.
5. Kossoff EH, Ritzl EK, Politsky JM, Murro AM, Smith JR, Duckrow RB, Spencer DD, Bergey GK. Effect of an external responsive neurostimulator on seizures and electrographic discharges during subdural electrode monitoring. *Epilepsia* 2004;45:1560–1567.
6. Osorio I, Frei MG, Sunderam S, Giftakis J, Bhavaraju NC, Schaffner SF, Wilkinson SB. Automated seizure abatement in humans using electrical stimulation. *Ann Neurol* 2005;57:258–268.
7. Sun FT, Morrell MJ, Wharen RE Jr. Responsive cortical stimulation for the treatment of epilepsy. *Neurotherapeutics* 2008;5:68–74.
8. Hamer HM, Morris HH, Mascha EJ, Karafa MT, Bingaman WE, Bej MD, Burgess RC, Dinner DS, Foldvary NR, Hahn JF, Kotagal P, Najm I, Wyllie E, Lüders HO. Complications of invasive video-EEG monitoring with subdural grid electrodes. *Neurology* 2002;58:97–103.
9. Katarivala NM, Bakay RA, Pennell PB, Olson LD, Henry TR, Epstein CM. Remission of intractable partial epilepsy following implantation of intracranial electrodes. *Neurology* 2001;57:1505–1507.
10. Ojemann GA. Multiple subpial transections are not effective or useful. In: *Epilepsy Surgery: Principles and Controversies*. (Miller JW, Silberberg DL, eds.) New York: Taylor and Francis, 2006:529–531.



American Epilepsy Society

Epilepsy Currents Journal

Disclosure of Potential Conflicts of Interest

Instructions

The purpose of this form is to provide readers of your manuscript with information about your other interests that could influence how they receive and understand your work. Each author should submit a separate form and is responsible for the accuracy and completeness of the submitted information. The form is in four parts.

1. Identifying information.

Enter your full name. If you are NOT the main contributing author, please check the box “no” and enter the name of the main contributing author in the space that appears. Provide the requested manuscript information.

2. The work under consideration for publication.

This section asks for information about the work that you have submitted for publication. The time frame for this reporting is that of the work itself, from the initial conception and planning to the present. The requested information is about resources that you received, either directly or indirectly (via your institution), to enable you to complete the work. Checking “No” means that you did the work without receiving any financial support from any third party – that is, the work was supported by funds from the same institution that pays your salary and that institution did not receive third-party funds with which to pay you. If you or your institution received funds from a third party to support the work, such as a government granting agency, charitable foundation or commercial sponsor, check “Yes”. Then complete the appropriate boxes to indicate the type of support and whether the payment went to you, or to your institution, or both.

3. Relevant financial activities outside the submitted work.

This section asks about your financial relationships with entities in the bio-medical arena that could be perceived to influence, or that give the appearance of potentially influencing, what you wrote in the submitted work. For example, if your article is about testing an epidermal growth factor receptor (EGFR) antagonist in lung cancer, you should report all associations with entities pursuing diagnostic or therapeutic strategies in cancer in general, not just in the area of EGFR or lung cancer.

Report all sources of revenue paid (or promised to be paid) directly to you or your institution on your behalf over the 36 months prior to submission of the work. This should include all monies from sources with relevance to the submitted work, not just monies from the entity that sponsored the research. Please note that your interactions with the work’s sponsor that are outside the submitted work should also be listed here. If there is any question, it is usually better to disclose a relationship than not to do so.

For grants you have received for work outside the submitted work, you should disclose support ONLY from entities that could be perceived to be affected financially by the published work, such as drug companies, or foundations supported by entities that could be perceived to have a financial stake in the outcome. Public funding sources, such as government agencies, charitable foundations or academic institutions, need not be disclosed. For example, if a government agency sponsored a study in which you have been involved and drugs were provided by a pharmaceutical company, you need only list the pharmaceutical company.

4. Other relationships

Use this section to report other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work.



American Epilepsy Society

Epilepsy Currents Journal

Disclosure of Potential Conflicts of Interest

Section #1 Identifying Information

1. Today's Date: 3/12/12
2. First Name John Last Name Miller Degree MD, PhD
3. Are you the Main Assigned Author? Yes No

If no, enter your name as co-author:

4. Manuscript/Article Title: Responsive Cortical Stimulation: The 21% Solution?
5. Journal Issue you are submitting for: 12.3

Section #2 The Work Under Consideration for Publication

Did you or your institution at any time receive payment or services from a third party for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Complete each row by checking "No" or providing the requested information. If you have more than one relationship just add rows to this table.

Type	No	Money Paid to You	Money to Your Institution*	Name of Entity	Comments**
1. Grant	<input checked="" type="checkbox"/>				
2. Consulting fee or honorarium	<input checked="" type="checkbox"/>				
3. Support for travel to meetings for the study or other purposes	<input checked="" type="checkbox"/>				
4. Fees for participating in review activities such as data monitoring boards, statistical analysis, end point committees, and the like	<input checked="" type="checkbox"/>				
5. Payment for writing or reviewing the manuscript	<input checked="" type="checkbox"/>				
6. Provision of writing assistance, medicines, equipment, or administrative support.	<input checked="" type="checkbox"/>				
7. Other	<input checked="" type="checkbox"/>				

* This means money that your institution received for your efforts on this study.

** Use this section to provide any needed explanation.

Section #3 Relevant financial activities outside the submitted work.

Place a check in the appropriate boxes in the table to indicate whether you have financial relationships (regardless of amount of compensation) with entities as described in the instructions. Use one line for each entity; add as many lines as you need by clicking the “Add” box. You should report relationships that were present during the 36 months prior to submission.

Complete each row by checking “No” or providing the requested information. If you have more than one relationship just add rows to this table.

Type of relationship (in alphabetical order)	No	Money Paid to You	Money to Your Institution*	Name of Entity	Comments**
1. Board membership	<input checked="" type="checkbox"/>				
2. Consultancy	<input checked="" type="checkbox"/>				
3. Employment	<input checked="" type="checkbox"/>				
4. Expert testimony	<input checked="" type="checkbox"/>				
5. Grants/grants pending	<input type="checkbox"/>		Yes	NIH, CDC, Sunovian, UCB, Esai, Pfizer	ROSE study, Project Uplift, Investigational antiepileptic medication trials
6. Payment for lectures including service on speakers bureaus	<input checked="" type="checkbox"/>				
7. Payment for manuscript preparation.	<input checked="" type="checkbox"/>				
8. Patents (planned, pending or issued)	<input checked="" type="checkbox"/>				
9. Royalties	<input checked="" type="checkbox"/>				
10. Payment for development of educational presentations	<input checked="" type="checkbox"/>				
11. Stock/stock options	<input checked="" type="checkbox"/>				
12. Travel/accommodations/meeting expenses unrelated to activities listed.**	<input checked="" type="checkbox"/>				
13. Other (err on the side of full disclosure)	<input type="checkbox"/>				

* This means money that your institution received for your efforts.

** For example, if you report a consultancy above there is no need to report travel related to that consultancy on this line.

Section #4 Other relationships

Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?

No other relationships/conditions/circumstances that present a potential conflict of interest.

Yes, the following relationships/conditions/circumstances are present:

John W. Miller

Thank you for your assistance.
Epilepsy Currents Editorial Board