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Brain-responsive neurostimulation for epilepsy (RNS® System)

Tara L. Skarpaas[a,*], Beata Jarosiewicz[a], Martha J. Morrell[a,b]

[a] NeuroPace, Inc., Mountain View, CA, United States
[b] Department of Neurology and Neurological Sciences, Stanford University, Stanford, CA, United States

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ABSTRACT

Controlled clinical trials in adults with medically intractable focal seizures treated with the RNS® System demonstrate that closed-loop responsive neurostimulation to the seizure focus reduces the frequency of disabling seizures, is well tolerated, and is acceptably safe. Seizure reductions begin with initiation of treatment and continue over time, reaching median reductions of 75% after 9 years of treatment. Treatment with responsive cortical stimulation is also associated with improvement in quality of life and cognitive function related to the functional area being treated. In addition, the RNS System's chronic ambulatory electrocorticographic monitoring provides unprecedented insight into each patient's disease management, and into the study of epilepsy itself, in ways that may enhance the treatment of epilepsy in the future.

1. Introduction and rationale for development

About a third of patients with epilepsy have seizures that are resistant to medication. For many of these patients resective and/or ablative epilepsy surgery offer the best opportunity for seizure freedom. However, not all patients are candidates for these surgical procedures due to the risk of neurological deficits or they are unwilling to consider resective or ablative procedures. Designed to help these patients, the first implantable brain-responsive neurostimulator, the RNS® System, was approved in the U.S. in late 2013 as an adjunctive therapy in adults with medically uncontrolled focal onset seizures localized to one or two epileptogenic foci. In contrast to open-loop approaches to neuromodulation, in which therapy is delivered continuously or on a fixed schedule, the RNS System continuously monitors neural activity at the seizure focus and responds with stimulation only when epileptiform activity is detected.

2. Technical and functional characteristics

The implantable components of the RNS System (Fig. 1) include a cranially seated neurostimulator connected to 1 or 2 depth and/or cortical strip leads, each containing 4 electrode contacts, which are surgically placed at the seizure foci. The external components of the system include a RNS® Tablet ("Programmer") for physician use and a Remote Monitor for patient (home) use. Using the tablet, the physician programs detection and stimulation settings and retrieves and reviews data provided by the neurostimulator (such as samples of brain activity, battery measurements, lead impedances, programmed settings, and times and dates of detections and stimulations). Up to 12 min of 4-channel electrocorticographic activity can be stored in the neurostimulator at any one time. The patient transfers data from the neurostimulator to the home-use remote monitor, which clears neurostimulator memory for additional ECoG storage. Patient data are transmitted over the internet from the programmer and the remote monitor to a secure database called the Patient Data Management System (PDMS), where they are available for physician review.

The neurostimulator continuously senses and monitors electrocorticographic activity at the seizure focus and provides responsive electrical stimulation when abnormal patterns are detected. Detection settings are tailored to each individual patient by the physician, who programs detection using built-in tools such as a line length detector, abrupt changes in power in specific frequency bands, etc.

The physician also tailors responsive stimulation for each patient, and fine-tunes its parameters within a range of recommended settings according to the patient's report of their clinical response as well as the quantitative electrographic data that the device provides. Stimulation consists of current-controlled, charge-balanced biphasic pulses through any combination of the 8 electrodes and the neurostimulator housing. The physician programs the stimulation pathway and the stimulation frequency (1–333 Hz), current (0.5–12 mA), pulse width (40–1000 μs), and burst duration (10–5000 ms). The most common stimulation settings in the clinical trials were 100–200 Hz stimulation frequency, 1.5–3 mA current, 160 μs pulse width, and 100–200 ms burst duration. Once an initial detection and stimulation occurs, the neurostimulator

* Corresponding author at: 455N. Bernardo Avenue, Mountain View, CA, 94043, United States.
E-mail address: tskarpaas@neuropace.com (T.L. Skarpaas).

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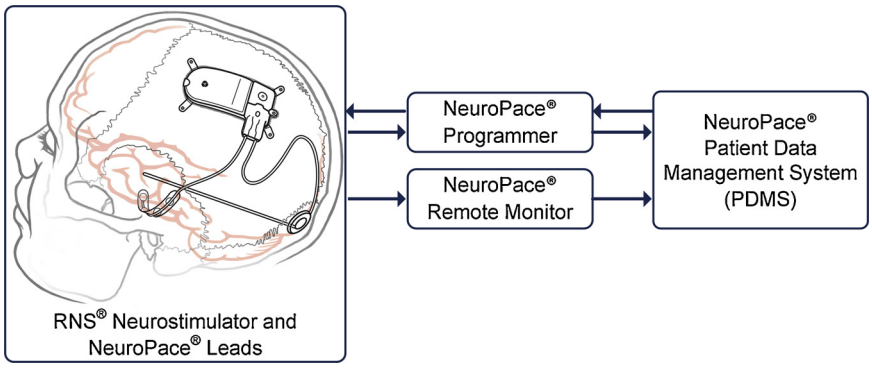

Fig. 1. Legend. The RNS® System.
The implantable components of the RNS System include a neurostimulator and leads for recording and stimulation (these can be depth and/or cortical strip leads, selected based on the target). The RNS® Tablet (previously referred to as NeuroPace® Programmer) contains proprietary software and communicates with the neurostimulator using a custom telemetry component (Wand). The programmer retrieves data stored on the neurostimulator and is used by the physician to program neurostimulator detection and stimulation settings. The remote monitor is a home-use monitoring device for the patient to retrieve data stored on the neurostimulator using the Wand and upload it to the Patient Data Management System (PDMS), a centralized database that stores the data uploaded from the programmer and remote monitor. Neurostimulator data and detection settings can also be transferred from PDMS to the programmer.

can provide an additional 4 stimulations if the detected activity does not resolve. Each stimulation consists of 2 bursts that are individually programmable, providing the opportunity for several different types of stimulation within a single abnormal electrocorticographic discharge. Usually, patients had 600–2000 detections (and therefore stimulations) per day. At typical burst durations, this adds up to less than 6 min of stimulation per day. With typical stimulation settings, the battery longevity is estimated at 8.4 years (NeuroPace RNS System Physician Manual - RNS-320, 2018), at which time the neurostimulator is replaced through a scalp incision in an outpatient procedure.

3. Results

3.1. Clinical safety and effectiveness

The RNS System was studied in three clinical trials: a 2-year primarily open-label Feasibility study (N = 65); a 2-year randomized controlled Pivotal study (N = 191); and a 7 year open-label Long-term Treatment study (N = 230) for patients completing the Feasibility or Pivotal studies. In total, 256 patients were implanted during the RNS System trials.

The multi-center double-blinded randomized controlled Pivotal study demonstrated the safety and effectiveness of the RNS System for its indicated use. Over 3 months of the blinded period, the overall reduction in disabling seizure (defined as focal motor, focal impaired awareness, and/or focal to bilateral tonic-clonic seizures) frequency in the treated patients (37.9%) was significantly larger than in the sham patients (17.3%; p = 0.012) (Morrell, 2011). In the month after the implant procedure (before stimulation was enabled), seizure frequency revealed a transient reduction in seizures of about 25%. Thereafter, the seizure rates continued to decrease in the stimulation-treated patients, whereas the non-treated patients gradually approached their pre-implant seizure frequency. By the final month of the blinded period (5 months after implant), patients treated with responsive stimulation had a significantly larger seizure frequency reduction (41.5%) than the sham stimulated patients (9.4%; GEE estimate, p = 0.008) (Morrell, 2011).

During the open-label period of the Pivotal trial and the follow-on open label Long-Term Treatment trial, all patients received responsive stimulation, and their seizure rates continued to decrease (Heck et al., 2014). The median reduction in seizure frequency was 44% at 1 year, 53% at 2 years (Heck et al., 2014), 60–66% at years 3–6 (Bergey et al., 2015), and 75% at year 9 (Nair and Morrell, 2018). A last observation carried forward analysis indicated that these results were not attributable to patient discontinuations. Twenty-eight percent of subjects had at least 1 seizure-free period of 6 months and 18% had 1 year or longer without seizures (Nair and Morrell, 2018). There were no differences in response based on the region of seizure onset (e.g. mesial temporal vs. neocortical) (Geller et al., 2017; Jobst et al., 2017), and the improvements in seizure control did not correlate with changes in antiepileptic medications (Heck et al., 2014; Bergey et al., 2015).

3.2. Tolerability and safety

Serious adverse events during treatment with the RNS System were no worse than with implantation of intracranial electrodes, with epilepsy surgery, or with treatment of Parkinson's disease with deep brain stimulation. Stimulation was well-tolerated, and there was no difference in the frequency or type of serious adverse events between the treated and sham groups over the blinded period (Morrell, 2011). Device-related serious adverse events over two years included infection at the implant site (3.7% of subjects), lead damage (2.6% of subjects), and lead revisions (3.7% of subjects) (Heck et al., 2014). The rate of infection was 3.7% per neurostimulator procedure (n = 31/840; implant or replacement) and the risk of infection did not change significantly as the number of procedures per patient increased (p = 0.66) (Weber et al., 2017). In addition, the SUDEP rate was 2 (95% C.I.: 0.7–5.2) per 1000 patient-stimulation years, which is favorable relative to that of treatment-resistant epilepsy patients in the placebo arm of adjunctive drug studies and of patients who continue to have seizures after resective surgery (Devinsky et al., 2018).

Quality of life (QOL) is a measure of the general well-being of an individual that incorporates the emotional, social, and physical aspects of the person's life. After one and two years of treatment with the RNS system, QOL significantly improved, particularly in domains that are specific to epilepsy and to cognitive function (Meador et al., 2015). QOL improvements were not as high as for patients with medically intractable focal seizures who achieve seizure freedom after an epilepsy surgery, but were higher than for medically intractable patients who are not candidates for epilepsy surgery and continue to be treated with best medical care.

Furthermore, there was no overall risk to mood (Meador et al., 2015) or cognition (Loring et al., 2015with treatment with responsive neurostimulation; in fact, some patients experienced benefit. For instance, patients with seizures beginning in a neocortical focus, especially in the frontal lobe, had statistically significant improvements in verbal fluency, and patients with seizures of mesial temporal lobe onset had a statistically significant improvement in learning, delayed free recall, and recognition (Loring et al., 2015).

4. Planned studies

4.1. Advantages of chronic ambulatory electrocorticographic monitoring

An important benefit of the RNS System is that it automatically records snapshots of electrocorticographic activity and keeps track of

the number of abnormal electrographic events that are detected hourly and daily for as long as the patient is treated with the system. This chronic ambulatory electrographic monitoring is primarily used to identify patient-specific temporal dynamics in epileptiform activity that can be used to individualize detection and stimulation, but it also provides the physician with unprecedented insight into the patient's ongoing treatment in a number of other ways.

For example, the electrocorticographic data provided by the RNS System can supplement information obtained in the acute inpatient epilepsy monitoring unit (EMU), which provides data that are obtained in a non-representative setting over a small period of time (with AEDs withheld, in a hospital bed with disrupted sleep, etc.), and may differ substantially from the patient's brain activity profile when they are going about their normal life for months and even years. For instance, case reports have demonstrated the value of chronic ambulatory electrocorticography for identifying patients who were likely to benefit from resection, even if they were initially thought not to be resection candidates based on acute EMU data (DiLorenzo et al., 2014; Enatsu et al., 2012). Similarly, about 13% patients in the randomized controlled pivotal trial who were thought to have bilateral mesial temporal onsets at enrollment based on EMU monitoring were actually found, after years of recording with the RNS System, to have only unilateral seizures when taking their usual medication and living their usual life (King-Stephens et al., 2015). In addition, for other patients, many days (average 41.6 days) of ambulatory data were required in order to determine that seizures arose bilaterally (King-Stephens et al., 2015), a recording duration well beyond the typical EMU stay.

The ambulatory data provided by the RNS System may also be used to help the physician identify and titrate effective antiepileptic medications. A challenge in optimizing medications for patients with epilepsy, particularly in refractory cases, is the amount of time it takes to identify which regimens are effective or ineffective. Recent studies have demonstrated that the data recorded by the RNS System could provide an early indication of whether the addition of an AED will be followed by a clinically meaningful reduction in seizure frequency (Mercier et al., 2017; Skarpaas et al., 2018). Furthermore, Mercier and colleagues (Mercier et al., 2017) reported that changes in the number of events detected by the neurostimulator as early as 1–2 weeks after starting a new medication could predict the clinical response to the new AED.

Retrospective analyses of the ambulatory electrocorticographic data provided by the RNS System have shown that 98% of patients have circadian periodicities in electrographic seizures (Quigg et al., 2015; Spencer et al., 2016) and that these circadian cycles depend on the region of seizure onset. Within a patient, these circadian cycles are remarkably consistent. Recently, Baud and colleagues (Baud et al., 2018) demonstrated both circadian and multidien patterns in the number of events detected by the neurostimulator. They also demonstrated that these periodicities could be used to retrospectively identify patient-specific periods of heightened seizure risk. If periods of heightened risk can be identified prospectively as well, RNS System data could potentially provide a reliable daily seizure forecast that could help patients better manage their disease.

Ongoing research analyzing the data collected by the RNS System using traditional machine learning and deep learning is aimed at identifying optimal detection and stimulation parameters for individual patients and for patients with similar clinical and electrocorticographic characteristics.

5. Conclusions

Controlled clinical trials in adults with medically intractable focal seizures treated with the RNS® System demonstrate that closed-loop responsive neurostimulation to the seizure focus reduces the frequency of disabling seizures, is well tolerated, and is acceptably safe. Seizure frequency reductions begin with initiation of treatment and continue over time, reaching median reductions of 75% after 9 years of treatment. Treatment with responsive cortical stimulation is also associated with improvement in quality of life and cognitive function related to the functional area being treated. In addition, the RNS System's chronic ambulatory electrocorticographic monitoring provides unprecedented insight into each patient's disease management, and into the study of epilepsy itself, in ways that may enhance the treatment of epilepsy in the future.

Author disclosures

Drs. Tara L. Skarpaas, Beata Jarosiewicz, and Martha J Morrell are employees of and have equity ownership/stock options with NeuroPace Inc.

References

Baud, M.O., Kleen, J.K., Mirro, E.A., et al., 2018. Multi-day rhythms modulate seizure risk in epilepsy. Nat. Commun. 9 (88).

Bergey, G.K., Morrell, M.J., Mizrahi, E.M., et al., 2015. Long-term treatment with responsive brain stimulation in adults with refractory partial seizures. Neurology 84, 810–817.

Devinsky, O., Friedman, D., Duckrow, R.B., et al., 2018. Sudden unexpected death in epilepsy in patients treated with brain-responsive neurostimulation. Epilepsia 59, 555–561.

DiLorenzo, D.J., Mangubat, E.Z., Rossi, M.A., et al., 2014. Chronic unlimited recording electrocorticography-guided resective epilepsy surgery: technology-enabled enhanced fidelity in seizure focus localization with improved surgical efficacy. J. Neurosurg. 120, 1402–1414.

Enatsu, R., Alexopoulos, A., Bingaman, W., et al., 2012. Complementary effect of surgical resection and responsive brain stimulation in the treatment of bitemporal lobe epilepsy: a case report. Epilepsy Behav. 24, 513–516.

Geller, E.B., Skarpaas, T.L., Gross, R.E., et al., 2017. Brain-responsive neurostimulation in patients with medically intractable mesial temporal lobe epilepsy. Epilepsia 58, 994–1004.

Heck, C.N., King-Stephens, D., Massey, A.D., et al., 2014. 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 55, 432–441.

Jobst, B.C., Kapur, R., Barkley, G.L., et al., 2017. Brain-responsive neurostimulation in patients with medically intractable seizures arising from eloquent and other neocortical areas. Epilepsia 58, 1005–1014.

King-Stephens, D., Mirro, E., Weber, P.B., et al., 2015. Lateralization of mesial temporal lobe epilepsy with chronic ambulatory electrocorticography. Epilepsia 56, 959–967.

Loring, D.W., Kapur, R., Meador, K.J., et al., 2015. Differential neuropsychological outcomes following targeted responsive neurostimulation for partial-onset epilepsy. Epilepsia 56, 1836–1844.

Meador, K.J., Kapur, R., Loring, D.W., et al., 2015. Quality of life and mood in patients with medically intractable epilepsy treated with targeted responsive neurostimulation. Epilepsy Behav. 45, 242–247.

Mercier, M.R., Hirsch, L.J., Duckrow, R.B., et al., 2017. Early Changes in Responsive Neurostimulation Detection Rates After Introduction of Anti-seizure Drugs Predict Efficacy. AES. Annual Meeting Abstract Database; AESnet.org.

Morrell, M.J., 2011. Responsive cortical stimulation for the treatment of medically intractable partial epilepsy. Neurology 77, 1295–1304.

Nair, D., Morrell, M.J., 2018. RNS System Investigators. Nine-year Prospective Safety and Effectiveness Outcomes From the Long-term Treatment Trial of the RNS® System. AES. Annual Meeting Abstract Database; AESnet.org.

NeuroPace RNS System Physician Manual - RNS-320, 2018. NeuroPace RNS System Physician Manual - RNS-320. https://www.neuropace.com/manuals/.

Quigg, M., Sun, F., Fountain, N.B., et al., 2015. Interrater reliability in interpretation of electrocorticographic seizure detections of the responsive neurostimulator. Epilepsia 56, 968–971.

Skarpaas, T.L., Tcheng, T.K., Morrell, M.J., 2018. Clinical and electrocorticographic response to antiepileptic drugs in patients treated with responsive stimulation. Epilepsy Behav. 83, 192–200.

Spencer, D.C., Sun, F.T., Brown, S.N., et al., 2016. Circadian and ultradian patterns of epileptiform discharges differ by seizure-onset location during long-term ambulatory intracranial monitoring. Epilepsia 57, 1495–1502.

Weber, P.B., Kapur, R., Gwinn, R.P., et al., 2017. Infection and Erosion Rates in Trials of a Cranially Implanted Neurostimulator Do Not Increase with Subsequent Neurostimulator Placements. Stereotact. Funct. Neurosurg. 95, 325–329.