doi: 10.2176/nmc.st.2020-0172
Neurol Med Chir (Tokyo) 61, 1–11, 2021
Online December 2, 2020

Responsive Neurostimulation as a Novel Palliative Option in Epilepsy Surgery

Motoki INAJI,[1] Takamichi YAMAMOTO,[2] Kensuke KAWAI,[3] Taketoshi MAEHARA,[1] and Werner K. DOYLE[4]

[1]*Department of Neurosurgery, Tokyo Medical and Dental University, Tokyo, Japan*
[2]*Department of Neurosurgery, Comprehensive Epilepsy Center, Seirei Hamamatsu General Hospital, Hamamatsu, Shizuoka, Japan*
[3]*Department of Neurosurgery, Jichi Medical University, Shimotsuke, Tochigi, Japan*
[4]*Department of Neurosurgery, NYU Langone Medical Center, New York, NY, USA*

Abstract

Patients with drug-resistant focal onset epilepsy are not always suitable candidates for resective surgery, a definitive intervention to control their seizures. The alternative surgical treatment for these patients in Japan has been vagus nerve stimulation (VNS). Besides VNS, epileptologists in the United States can choose a novel palliative option called responsive neurostimulation (RNS), a closed-loop neuromodulation system approved by the US Food and Drug Administration in 2013. The RNS System continuously monitors neural electroencephalography (EEG) activity at the possible seizure onset zone (SOZ) where electrodes are placed and responds with electrical stimulation when a pre-defined epileptic activity is detected. The controlled clinical trials in the United States have demonstrated long-term utility and safety of the RNS System. Seizure reduction rates have continued to improve over time, reaching 75% over 9 years of treatment. The incidence of implant-site infection, the most frequent device-related adverse event, is similar to those of other neuromodulation devices. The RNS System has shown favorable efficacy for both mesial temporal lobe epilepsy (TLE) and neocortical epilepsy of the eloquent cortex. Another unique advantage of the RNS System is its ability to provide chronic monitoring of ambulatory electrocorticography (ECoG). Valuable information obtained from ECoG monitoring provides a better understanding of the state of epilepsy in each patient and improves clinical management. This article reviews the developmental history, structure, and clinical utility of the RNS System, and discusses its indications as a novel palliative option for drug-resistant epilepsy.

Keywords: responsive neurostimulation, closed-loop system, palliative treatment, drug-resistant epilepsy, focal onset epilepsy

Introduction

About 30–40% of patients with epilepsy are unresponsive to medication and continue to experience seizures.[1–3] These patients with drug-resistant epilepsy may have epilepsy with multiple or bilateral independent foci, diffuse lesions, or a focus on the eloquent cortex. Consequently, they are not always suitable candidates for resective surgery, a definitive intervention with the possibility to achieve seizure freedom.[4,5] Furthermore, the status of seizure freedom obtained by focus resection is maintained for a long period of time in only 50%–70% of patients, notwithstanding preoperative multi-modality surveys and invasive monitoring with intracranial electrodes to successfully locate a seizure onset zone (SOZ).[6,7]

Vagus nerve stimulation (VNS) has been the palliative option with an implantable device in Japan for patients who are not adapted candidates for intracranial epilepsy surgery or patients in whom the previous surgical procedure has failed. The outcome of its efficacy, defined as a mean seizure reduction of at least 50%, has been demonstrated in only 50%–60% of patients treated with VNS.[8] Hence, alternative surgical options are necessary to improve

Received June 1, 2020; Accepted September 17, 2020

the overall outcome including seizure reduction and quality of life for patients with drug-resistant epilepsy.

A novel neuromodulation system characterized by direct seizure detection in the skull and direct stimulation to the brain was developed in the United States over the last two decades.[9] An implantable brain-responsive neurostimulator, the RNS System (Responsive Neurostimulation System; NeuroPace, Inc., Mountain View, CA, USA), was approved by the US Food and Drug Administration in 2013.[10,11] The RNS System is an adjunctive therapy for adults with medically uncontrolled focal onset seizures localized to one or two epileptogenic foci. This system is the first-ever closed-loop neuromodulation device for epilepsy. It continuously monitors neural activity at or within 2 cm of the seizure foci, and responds with electrical stimulation when epileptiform activity is detected. This article reviews the developmental history, structure and clinical utility of the RNS System and discusses its indications as a novel palliative option for drug-resistant epilepsy.

Developmental History of the RNS System

Morrell et al. described development of the RNS System in detail.[12] According to the first report of direct stimulation to the human brain cortex, published by Penfield in the 1950s, electrical stimulation attenuated both spontaneous epileptic discharge and normal activity.[13] The approach by Penfield formed the basic concept of neuromodulation therapy applied to epilepsy. Further studies based on the concept, both basic and clinical, were conducted to develop neuromodulation devices for epilepsy treatment. Both an open-loop system and a closed-loop system were developed for targeting both localization-related and generalized epilepsy.[12,14,15] The first chronic brain stimulation system for epilepsy was developed in the 1990s, and adopted an open-loop system to administer an electrical brain stimulation according to a fixed schedule independent of epileptic and spontaneous brain physiological activities.[15] The early targets for stimulation were not epileptic foci. Distant deep brain structures such as the cerebellum, thalamus, and basal ganglia were primarily stimulated.[15] The targets of open-loop stimulation in more recent trials have included epileptogenic regions such as the mesial temporal structures and the primary motor cortex.[15]

Closed-looped neuromodulation systems suppress electrographic seizures by direct brain stimulation in response to detected electrographic abnormalities. In the research described by Psatta et al. in 1983, responsive stimulation was more effective than non-responsive (i.e., continuous) in suppressing epileptic activity in an experimental cat model.[16] In the same experiments, responsive stimulation was more effective when less time passed between detection of epileptic discharges and brain stimulation. These reports suggested that a closed-loop system would become a preferred neuromodulation method for epilepsy treatment.

In experiments from the 1990s, Lesser et al. demonstrated that direct cortical stimulation for a short duration effectively suppressed after-discharges in humans.[17] Motamedi et al. found that early and direct stimulations to a SOZ were the most effective means of terminating after-discharges.[18] These results suggested that direct responsive stimulation to epileptic foci could effectively terminate propagation of electrographic seizures.

The development of such devices for clinical practice, however, is time-consuming and technologically complex. A closed-loop system requires real-time analysis of ECoG data and a feedback control system for automatic delivery of responsive stimulation when a seizure event is detected. Early in its development, around 2000, the prototype of a responsive stimulation system required a large bedside unit housing an electroencephalography (EEG) machine, computer controllers, and stimulator hardware [19,20]. If the device was to be small enough and to last long enough to be both completely implantable and clinically useful, it had to consume little power, which, in turn, necessitated simple detection algorithms. The early studies also provided preliminary evidence that high-frequency responsive stimulation to a SOZ was effective for seizure control. Moreover, responsive stimulation only controlled seizures when specific temporal, that is, stimulation early during a seizure, and spatial, that is, stimulation within 2 cm from a SOZ, requirements were satisfied. Based upon these early findings, the RNS System was developed in 2005 as the first-ever implantable device with a closed-loop system to effectively treat epileptic foci by responsive stimulation.

The Structure of the RNS System

The RNS System consists of one set of components implanted intracranially and one set of components operated externally. Physicians and patients use the external components to communicate and interact with the implanted device.[10,11,21,22] The implantable components of the RNS System include a neurostimulator and two electrode arrays that can be either depth and/or strip arrays in any combination. Each of the electrode arrays has four electrode contacts (Fig. 1A). Physicians access the neurostimulator via an RNS tablet (the "Programmer"), while patients at home access the device using a home-use remote monitor (the "Remote Monitor") (Fig. 1B). The

Fig. 1 (A) The neurostimulator and a strip lead. (B) The tablet for physician use and the wand used to access the neurostimulator.

neurostimulator contains a set of electronics components and battery (Fig. 2). The device is surgically embedded into the cranium, flush with the skull surface. At least two electrode arrays (also referred to as "electrode leads") are attached to the neurostimulator, though a few more leads are usually implanted for potential future use, especially if the two initially chosen leads fail to identify or modulate ictal onsets with sufficient efficacy. The subdural strip array consists of four disc-shaped electrodes with contacts measuring 3.18 mm in diameter, spaced apart at 10 mm intervals.[21,23] The depth electrode arrays consist of four cylindrical contacts measuring 1.27 mm in diameter, spaced apart at intervals of either 10 mm or 3.5 mm.[21,23] A surface area of 7.9 mm^2 is left exposed on the contacts of both the depth and subdural electrodes.[21,23] Several cable lengths associated with the strip or depth electrode leads permit surgical flexibility for intracranial electrode placement and target locations relative to the location of the implanted generator within the skull. The leads are inserted through burr holes or skull windows with the aid of a stereotactic or frameless navigation system to set the electrode trajectories and target the epileptic foci (SOZ) previously determined by presurgical evaluation or previous invasive monitoring with intracranial electrodes. The RNS device continuously senses and monitors electrocorticography (ECoG) data at or near the SOZ and provides responsive electrical stimulation when abnormal and predetermined ECoG patterns are detected. Detection settings for abnormal seizure patterns are tailored to each individual patient by a physician through periodic empirical programming of detection and stimulation parameters over the initial course following implantation.

A physician programs both detection and stimulation settings and reviews a patient's log data from the RNS System via a smart device tablet that communicates with the implanted device. Up to 12 minutes of four-bipolar channels of ECoG data can be stored in the neurostimulator at any one time.[12–14] A few times a week, a patient transfers the stored data from the RNS System to the Remote Monitor, which resets a memory of the device for future ECoG storage. To prevent overwriting of old ECoG data with new ECoG recordings, each patient is encouraged to download the data daily from the device. Patient data are transmitted securely, satisfying patients' privacy requirements, from the Remote Monitor to a secure cloud-based database called the Patient Data Management System (PDMS), where they are available for remote physician review via the Internet.[21–23]

A physician tailors characterized programming of responsive stimulation specific to each patient, and needs fine-tuning based upon a patient's report of clinical responses and associated ECoG data. The electrical stimulation is a current-controlled, charge-balanced biphasic pulse transmitted through any combination of the eight implanted electrodes and the neurostimulator metallic housing. A physician can program the following parameters: stimulation pathway, stimulation frequency (1–333 Hz), stimulation current (0.5–12 mA), pulse width (40–1000 μsec), and burst duration (10–5000 msec). The most common stimulation settings used in the published clinical trials were as follows: 100–200 Hz stimulation frequency, 1.5–3 mA current, 160 μsec pulse width, and 100–200 msec burst duration.[10,21] A physician also has an option of setting another four stimulations if a primary setting fails to avert seizure

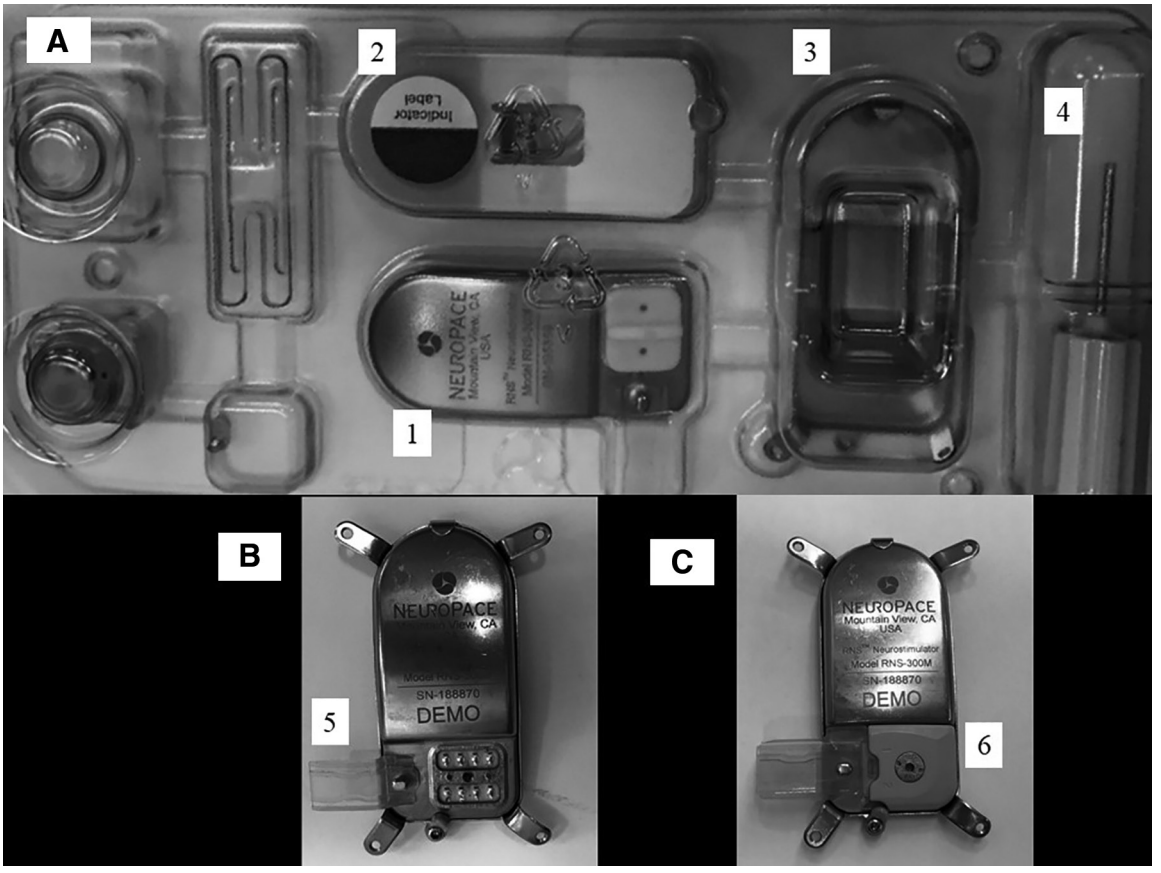

Fig. 2 (A) Neurostimulator kit. 1) Neurostimulator. 2) Craniectomy template. 3) Ferrule. 4) Wrench. (B) Neurostimulator without the connector cover. 5) Lead strain relief. (C) Neurostimulator with the connector cover. 6) Connector cover.

hypersynchrony. Each stimulation consists of two bursts, each of which can be individually programmed to permit several different stimulations against a single abnormal epileptic discharge. From 600 through 2000 detections and accompanying stimulations are typically recorded over a day in routine use. However, the duration of electrical stimulations adds up to less than 6 min per day.[21] When the battery of the implanted device expires, after an average of 8.4 years, the RNS System must be replaced through the previous scalp incision.[21]

Representative Case #1

The following two representative cases treated with the RNS System are demonstrated as experience at the NYU Langone Medical Center. The first case was a 25-year-old, right-handed man with epilepsy onset at the age of 15 years. His seizures presented as focal impaired awareness seizures (FIAS) characterized by receptive aphasia occurring up to 10 times a day. In very rare instances, he also experienced focal to bilateral tonic–clonic seizures (FBTCS). Scalp video-electroencephalography (vEEG) revealed broad left temporal seizure onsets. Brain computed tomography (CT), magnetic resonance imaging (MRI), and FDG-PET images were normal. Intracranial ECoG monitoring and functional mapping captured five habitual seizures. The SOZ was found to co-localize with the Wernicke's area in the left posterior superior temporal gyrus, and was verified by extra-operative functional mapping using the implanted electrodes. The RNS System was implanted 6 months after the intracranial ECoG survey via the left fronto-temporal craniotomy with a burr hole of the left occipital region (Fig. 3A). The depth electrode was inserted and targeted by frameless navigation. The electrode was placed into the left insular cortex from the occipital burr hole entry and fixed in place by a burr hole cap (Fig. 3B). A metal template outline of the implanted device was used to design the left fronto-temporal craniectomy to accommodate the ferrule that was to be subsequently fixed to the cranium by screws sitting precisely within the craniectomy (Fig. 3C). Before placing the ferrule, the dura was opened and three strip electrodes were placed on the left frontal and temporal cortex in locations that had been identified as the SOZ during the previous invasive ECoG survey

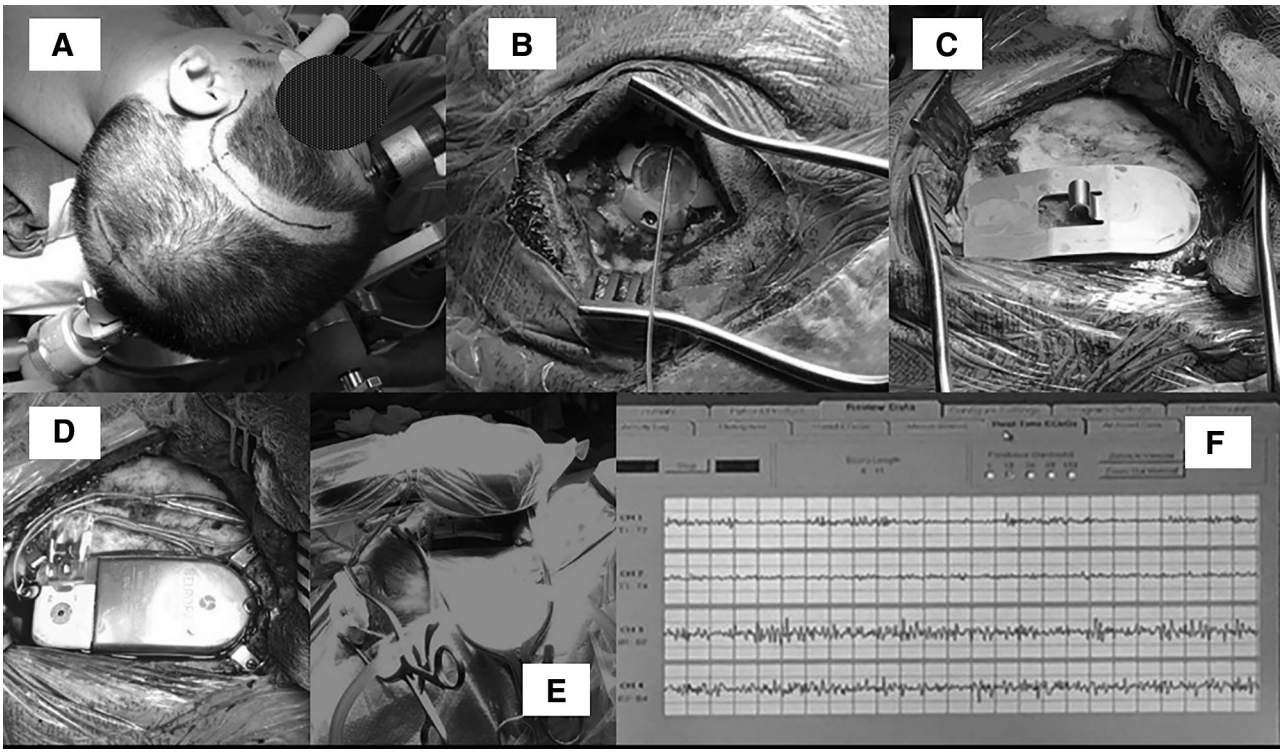

Fig. 3 (A) Skin incision of case #1. The left fronto-temporal craniectomy and occipital burr hole were opened. (B) The depth lead was fixed by the burr hole cap. (C) A metal template was used for the craniectomy. (D) Two selected leads were connected to the neurostimulator and placed on the anchored ferrule. (E) Access to the neurostimulator using the wand. (F) Intraoperative electroencephalography.

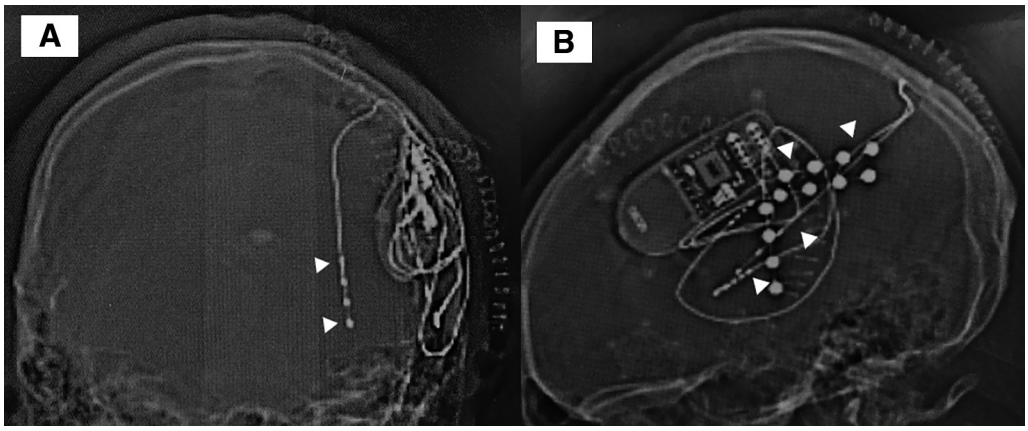

Fig. 4 Post-operative skull X-p of case #1. (A) AP view and (B) Lateral view. Two selected leads were connected to the stimulator (white arrow).

performed 6 months earlier (Fig. 4). After a total of four electrodes were placed, the electrodes were attached to the RNS System in different paired combinations and tested by ECoG. Based on the ECoG data and the preoperative information used to define the SOZ, two electrodes were selected for use. These two electrode leads were connected to the stimulator, and the other two leads were placed within protective sleeves to cover their contacts. The two leads not attached to the stimulator will be available for use in the future if the first two electrodes fail to sufficiently control or detect seizures (Figs. 3D–3F). The final steps of the procedure were to close the dura, implant the ferrule into the skull within the craniectomy site, secure the device into the ferrule, and close the scalp incision.

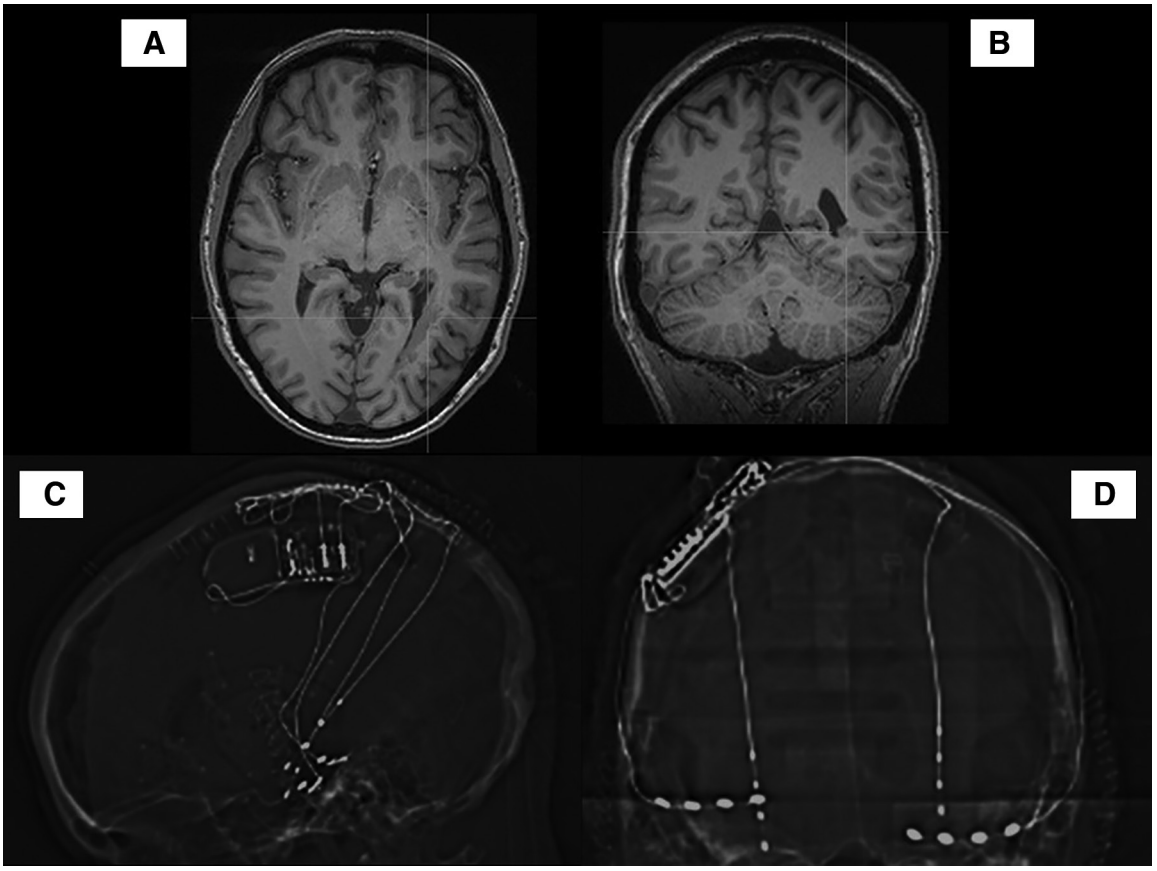

Fig. 5 Preoperative MRI images of case #2: (A) Axial View and (B) coronal view. The images show paraventricular heterotopia. Post-operative skull X-p of case #2: (C) Lateral view and (D) AP view.

Treatment with the RNS System is well tolerated in eloquent areas.[24,25] Because stimulation with high current intensities may nonetheless evoke discernible symptoms, patients should be asked to receive test stimulations during in-office programming visits to ensure tolerability.

Representative Case #2

A 49-year-old right-handed woman with drug-resistant epilepsy presented with several FIAS per week and rare FBTCS. A brain MRI revealed gray matter heterotopia at the occipital horn of the left lateral ventricle (Figs. 5A and 5B). Scalp vEEG captured bilateral independent anterior temporal seizures that occurred independently. RNS was selected for palliative management in place of resection, given the bitemporal status of her disease. Implantation of the RNS System was performed by placement of two depth electrodes via the separate right and left occipital burr holes into the hippocampus using frameless navigation for the targeting and trajectory. Two strip electrodes were additionally implanted under the bilateral temporal lobe base via the separate temporal burr holes. After the usual ECoG and preoperative analysis of the seizure onset information, the two depth electrodes implanted in the hippocampi were connected to the stimulator (Figs. 5C and 5D).

Intracranial monitoring is not always required prior to implantation of the RNS System, as exemplified by this second case of bilateral temporal lobe epilepsy (TLE). Although 59% of patients with the RNS System underwent intracranial ECoG monitoring prior to implantation, therapeutic effects were similar between these patients and patients who did not obtain prior ECoG monitoring.[25–29] In patients who have lesional bilateral TLE with concordant ictal recordings on scalp EEG, invasive intracranial ECoG monitoring can be spared often before implantation of the RNS System.

Efficacy and Safety of the RNS System in Clinical Trials

Three major clinical trials were carried out to investigate efficacy and safety of the RNS System. The first trial was a 2-year open-label feasibility study (N = 65). The second trial was a 2-year

randomized controlled pivotal study (N = 191). The third trial was a 7-year open-label long-term treatment study (N = 230) for patients who had completed the feasibility study or pivotal study.[11,12,25,27,29] In total, 256 patients received implantation of the device in the course of the three clinical trials.[11,12,25,27,29]

The pivotal study was the first multicenter, double-blind, randomized controlled trial conducted to assess effectiveness and safety of the RNS System for patients with drug-resistant and focal onset epilepsy.[27] Patients who participated in this study were 18–70 years of age, had focal onset seizures that were left uncontrolled in ≥2 trials of anti-epileptic drugs (AEDs), suffered 3≥ disabling seizures per month on average, and had up to two epileptogenic regions. The characteristics of patients showed mesial temporal onsets in 50% of them, multiple epileptic foci in 55%, history of prior therapeutic surgery for epilepsy without success in 32%, and previous VNS therapy in 34%.[27] Over the first 3 months of the blinded treatment phase, the overall outcome in seizure reduction demonstrated 37.9% in the group of treated patients as compared to only 17.3% in the group of sham patients ($p = 0.012$).[27] The difference between the two groups had widened at 5 months after implantation with disappearance of the lesioning effect. The reduction rate in seizure frequency was significantly better in the patients receiving stimulation by the RNS System than in the sham group (41.5% vs 9.4%, $p = 0.008$).[27] During the open-label period of the pivotal trial and the ensuing long-term treatment trial, all of the patients received responsive stimulation and experienced progressive decrease in their seizure rates.[25,29] The reduction rate in seizure frequency was 44% at 1 year, 53% at 2 years, 60–66% at 3–6 years, and 75% at 9 years.[21,25,29,30] Twenty-eight percent of the subjects had at least one seizure-free period of 6 months, and 18% had seizure-free periods of 1 year or longer.[21] The original concept of this device was to provide treatment of seizures in the peracute phase by electrically stimulating a SOZ to stop propagation of abnormal neuronal activities early in seizure onsets. However, the fact of progressive decrement in seizure frequency in clinical use suggests that the RNS System could make chronic neuroplasticity similar to that seen in VNS therapy. The RNS System may have a potential modifying epileptic network in patients with drug-resistant epilepsy.

A review of the published data shows no difference in the frequency of adverse events between the group of patients treated with the RNS System and the group of patients with sham treatment during the blinded treatment period in the pivotal trial.[27] Serious adverse events were reported only within the initial peri-operative implantation period, and there was no patient who suffered neurological deficits lasting for a long time. Over the mean follow-up period of 5.4 years, 9.4% of the patients suffered superficial implant site infections and 4.7% of them suffered intracranial hemorrhages without permanent neurological deficits.[24,31] Among the 12 cases with hemorrhagic complications, four events including two cases of epidural hematoma, one case of subdural hematoma, and one case of intraventricular hemorrhage occurred after implantation of the RNS System, and five other events occurred in the chronic period as consequences of seizures.

Lee et al. reported a single-center experience involving 40 surgeries for 10 patients. Their report described two procedures of incision and drainage for soft tissue infections and two revisions to correct lead damage.[31] Weber reported a detailed analysis of infections in 256 patients followed for the average of 7 years.[32] The infection rate was 3.7% per surgical procedure, and the rate of scalp erosion was 0.8%. The infection rates did not increase with subsequent surgical procedures, and a prior infection or erosion at the implant site did not significantly increase the infection risk in later procedures.[32] Overall, implantation of the RNS System is deemed to be a safe procedure, since its complication rates are not worse than those of other devices; for instance, deep brain stimulation for Parkinson's disease.

Long-term efficacy and safety of the RNS System have been separately analyzed in disease subgroups such as neocortical epilepsy and TLE. Neocortical epilepsy is an important target of the RNS System, especially when the SOZ is located in areas of the eloquent cortex such as the primary language and sensorimotor areas. Functional deficits associated with stimulation have never been reported in these cases. In the feasibility and pivotal trials, 126 patients with neocortical epilepsy were treated and followed for the average of 6 years.[24] Patients in this group obtained a 58% median seizure reduction, and the responder rate with more than a 50% seizure reduction was 55%. Further detailed analyses based on locations of SOZ showed a median seizure reduction of 70% for seizures from both the frontal lobe and the parietal lobe. Patients with neocortical epilepsy of the temporal lobe achieved a 58% median seizure reduction, and patients with multilobar epilepsy also showed a 51% reduction.[24] Although both lesional and nonlesional patients who underwent an MRI study benefited from this treatment, seizure reduction was greater in patients with a structural lesion (77%), as compared to patients without an obvious lesion by neuroimaging (45%).[24] During the open-label period, 37% of patients had at least one seizure-free interval lasting

3 months or longer, 26% had at least one lasting ≥6 months, and 14% had at least one lasting ≥1 year.[24] Fifty-two percent of patients with neocortical epilepsy had undergone prior intracranial epilepsy surgery. A review of these cases showed no difference in response to treatment with the RNS System between the patients with and without prior surgery.[24]

Geller also reported efficacy of the RNS System in patients with mesial temporal lobe epilepsy (MTLE).[30] A total of 111 cases with MTLE were investigated. Among them, 72% had bilateral mesial temporal lobe (MTL) onsets and 28% had unilateral onsets.[30] Seventy-six patients had only two depth leads placed, 29 had both depth and strip leads, and 6 received only two strip leads. The median percent in seizure reduction reached 70% over the follow-up period of 6.1±2.2 years. Twenty-nine percent of patients with MTLE experienced at least one seizure-free interval lasting 6 months or longer, and another 15% had 1 year or longer. No difference in seizure control was observed among patients with and without mesial temporal sclerosis, bilateral MTL onsets, prior resection, prior intracranial monitoring, and prior VNS. Seizure reduction in this study, moreover, was not dependent on the location of depth leads relative to the hippocampus. It is suggested that leads for stimulation are not necessarily placed precisely within the hippocampus, since stimulation was as effective when MTL leads were placed within the hippocampus or nearby. However, future research will be obligatory to explore this experience in responsive MTL stimulation.[30]

In a report from Hirsh et al., 24 patients underwent MTL resections in 157 TLE patients who had been treated by the RNS System stimulating bilateral MTLs. The data obtained from chronic and ambulatory ECoG recording by the device showed that these patients might benefit from MTL resections.[33] These findings clearly demonstrated that chronic data from the RNS System provided sufficient evidence to pursue unilateral MTL resection in patients who had been presumed to suffer from bilateral MTLE. Seizure reduction on these patients at the last follow-up after MTL resection was 94%. Nine patients (38%) showed exclusively unilateral electrographic seizures, and became seizure-free after MTL resections. Fifteen (62%) out of 24 patients had bilateral MTL electrographic seizures and ultimately underwent MTL resections on the more active side of the temporal lobes. Eight of 15 patients obtained seizure freedom and the mean seizure reduction in 15 patients was 90% at the last follow-up. Twenty-one patients out of 24 patients were followed up for more than a year. Eight patients with unilateral MTLE and 7 (54%) out of 13 patients with bilateral MTLE kept free from seizures. These data suggest that chronic intracranial ECoG recordings provide information about correct lateralization of seizure onset and can identify potential patients who may benefit from additional resection.

In addition to reducing frequency of disabling seizures, the RNS System also reduced the risk of unexpected death and improved both quality of life (QOL) and cognitive function.[34–36] Devinsky et al. identified two possible, one probable, and four definite sudden unexpected deaths in epilepsy (SUDEP) events in an analysis of 14 deaths among 707 patients treated with the RNS System, that is, 2208 post-implantation years.[34] The SUDEP rate, 2 per 1,000 patient-stimulation years, was lower than the rate in patients with drug- or surgery-resistant epilepsy.[34] Improvements in QOL are reported after 2 years of this treatment, especially in the category of cognitive function.[35,36] Furthermore, no psychological or cognitive deterioration was reported in this treatment.[35,36] Patients with neocortical epilepsy, particularly frontal lobe epilepsy, showed significant improvements in the verbal fluency test. Similarly, patients with TLE showed remarkable improvements in learning, delayed free recall, and recognition tests.[35]

Indications for Treatment with the RNS System

The RNS System could meet incremental expectations for palliative therapy from many epilepsy patients who resist drug treatment and are not suitable candidates for resective surgery in Japan, as it has been observed in the United States. Although it is our estimation, this therapy would demonstrate capability to achieve almost complete seizure control in about 10%–15% of these patients with marked intractability.

Patients with bilateral MTLE and neocortical epilepsy of the eloquent cortex are ideal candidates for this therapy. Stereotactic implantation of depth leads via a posterior-to-anterior trajectory along the long axis of the hippocampus, with the distal electrode terminating in the hippocampal head, has been demonstrated as an important surgical strategy in implantation of the RNS System for patients with MTLE.[30,37] Insertion of depth leads in an accurate trajectory requires stereotactic techniques, either with a frameless navigation system, a stereotactic frame, or robotic assistance.

Surprisingly, the subgroup analysis of the pivotal study found that RNS System had equal effects on both unilateral and bilateral TLE, on both lesional and non-lesional epilepsy, and on cases both with and without previous temporal lobectomy.[30] As mentioned above, some cases with MTLE underwent MTL resections with information from chronic ECoG recordings readily provided by the RNS System.

From that standpoint, the diagnostic utility of the device was comparable to its therapeutic utility.[33]

Seizure outcomes after focal resection for neocortical epilepsy have historically been inferior to those of MTL surgery, since seizure freedom could be accomplished in less than 40%–60% of patients with neocortical epilepsy.[6,7] An epileptogenic area of the neocortex is occasionally located on or near the eloquent cortex, and then it does not allow complete resection. Consequently, the RNS System would offer some additional benefits in these patients with neocortical epilepsy or extra-TLE by providing neuromodulation on the remaining seizure focus.

A subset of candidates for the RNS System might also be candidates for VNS, and possibly for DBS of the anterior nucleus of the thalamus in some instances. The outcome in seizure reduction of each neurostimulation device seems to be similar, partly because trials have never been done to compare the relative clinical efficacy of VNS, RNS, and DBS. The specific indications of these devices may overlap each other. However, the structures and the mechanisms of action are totally different. VNS is least invasive among them, because it does not require direct approaches to the brain.

There are more differences between VNS and RNS. Whereas RNS is approved only for epilepsy patients with one or two seizure foci, VNS is approved for patients with multifocal or generalized epilepsy. VNS is approved without age restriction in Japan. The RNS System, meanwhile, is approved only in adults in the United States, though some researches have demonstrated efficacy in young patients.[38,39] It is allowed to take an MRI for patients with VNS except the neck and the upper body. The RNS System ultimately received a conditional safety approval for certain MRI studies in 2020. For these reasons, VNS may be a better option in children and in patients with generalized epilepsy. Combination therapy with VNS and RNS remains an option in patients who may already undergo VNS therapy and are currently being considered for RNS. The data are still too scarce to determine if such a dual modulation would really work for patients or would give better outcome than either therapy alone.

Chronic ECoG Monitoring by the RNS System

A unique advantage of the RNS System is its ability to record automatically and store ECoG data. The device can provide chronic ambulatory ECoG monitoring for empirical adjustments and to individualize parameters for seizure detection and electrical stimulation. This ECoG data may also offer detailed and unobtainable information that have a potential to influence treatment strategy including further surgical options.[21,23,33]

ECoG monitoring is one of the most essential evaluation methods for decision-making in diagnosis and treatment of epilepsy. Long-term scalp vEEG monitoring or ECoG monitoring with intracranial electrodes is performed at an epilepsy monitoring unit (EMU) when patients are hospitalized. Therefore, time of monitoring is limited for a week or two, and circumstances are different from their daily lives. These data do not necessarily reflect daily or usual brain activities in each patient. On the contrary, the RNS System provides ECoG data over months and even years under ordinary conditions.

In the pivotal trial, 13% of patients with bilateral MTLE diagnosed by previous monitoring at an EMU were actually revealed to have unilateral MTLE by this chronic ambulatory ECoG monitoring with the RNS System.[40] According to the chronic ECoG data of patients with bitemporal implantation of RNS leads, more than 40 days were required to record bilateral electrographic seizures.[40] This finding suggests that conventional diagnostic EEG methods at an EMU will fail to detect some bitemporal seizure onsets within the narrow time window of up to 2 weeks. Ambulatory ECoG data obtained by the RNS System may have a potential to change diagnostic approaches for some patients. Additionally, chronic ambulatory ECoG data may be useful for evaluating effectiveness of antiepileptic medications.[41,42] The data from the RNS System provide new indicators or biomarkers for evaluating epilepsy management.

Conclusions

The RNS System is a novel and closed-loop implantable neuromodulation device. Clinical trials have demonstrated that RNS is a safe and effective treatment option for patients with drug-resistant focal onset epilepsy including MTLE and neocortical epilepsy. The RNS System may be useful in patients who have prior resections without satisfactory results. In terms of a diagnostic role of the RNS System, the device provides chronic continuous ECoG monitoring to bring more information for better understanding of real seizure activities. The concept, structure, safety, and adverse events of the RNS System were reviewed in this article. This device will be a promising tool as one of the palliative options and make a substantial change in epileptology and neuroscience research.

Ethical Approval

All procedures conformed with the ethical standards of the institutional and/or national research committee, with the 1964 Helsinki Declaration and its later

amendments, or with comparable ethical standards. Informed consent was obtained from the patients described in this report.

Postscript

The first author visited the NYU Langone Medical Center to research epilepsy surgery with a focus on the RNS System, on a self-funding basis. Requests for RNS System approval have been officially submitted by three societies, namely, the JNS, the Japan Epilepsy Society, and the Epilepsy Surgery Society of Japan.

Conflicts of Interest Disclosure

The first author and four co-authors report no conflicts of interest (COI) regarding this article. All the Japanese authors are members of the Japan Neurosurgical Society (JNS) and have submitted COI declarations to the JNS Office in self-reported COI disclosure statements.

References

1) Kwan P, Arzimanoglou A, Berg AT, et al.: Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. *Epilepsia* 51: 1069–1077, 2010
2) Brodie MJ, Barry SJ, Bamagous GA, Norrie JD, Kwan P: Patterns of treatment response in newly diagnosed epilepsy. *Neurology* 78: 1548–1554, 2012
3) Kwan P, Brodie MJ: Early identification of refractory epilepsy. *N Engl J Med* 342: 314–319, 2000
4) Engel J Jr, Cascino GD, Shields WD: Surgically remediable syndromes. In: *Epilepsy: A Comprehensive Textbook*, ed 2. Philadelphia: Wolters Kluwer/Lippincott Williams & Wilkins, 2007, pp. 1761–1769
5) Engel J Jr, McDermott MP, Wiebe S, et al.: Early surgical therapy for drug-resistant temporal lobe epilepsy: a randomized trial. *JAMA* 307: 922–930, 2012
6) Engel J: Surgery for seizures. *N Engl J Med* 334: 647–652, 1996
7) Téllez-Zenteno JF, Dhar R, Wiebe S: Long-term seizure outcomes following epilepsy surgery: a systematic review and meta-analysis. *Brain* 128: 1188–1198, 2005
8) Kawai K, Tanaka T, Baba H, et al.: Outcome of vagus nerve stimulation for drug-resistant epilepsy: the first three years of a prospective Japanese registry. *Epileptic Disord* 19: 327–338, 2017
9) Li MCH, Cook MJ: Deep brain stimulation for drug-resistant epilepsy. *Epilepsia* 59: 273–290, 2018
10) Skarpaas TL, Jarosiewicz B, Morrell MJ: Brain-responsive neurostimulation for epilepsy (RNS® System). *Epilepsy Res* 153: 68–70, 2019
11) Sun FT, Morrell MJ: The RNS System: responsive cortical stimulation for the treatment of refractory partial epilepsy. *Expert Rev Med Devices* 11: 563–572, 2014
12) Morrell M: Brain stimulation for epilepsy: can scheduled or responsive neurostimulation stop seizures? *Curr Opin Neurol* 19: 164–168, 2006
13) Penfield W, Jasper H: Electrocorticography, in: *Epilepsy and the Functional Anatomy of the Human Brain*. Boston, Little, Brown: 1954, pp 692–738
14) Oommen J, Morrell M, Fisher RS: Experimental electrical stimulation therapy for epilepsy. *Curr Treat Options Neurol* 7: 261–271, 2005
15) Li Y, Mogul DJ: Electrical control of epileptic seizures. *J Clin Neurophysiol* 24: 197–204, 2007
16) Psatta DM: Control of chronic experimental focal epilepsy by feedback caudatum stimulations. *Epilepsia* 24: 444–454, 1983
17) Lesser RP, Kim SH, Beyderman L, et al.: Brief bursts of pulse stimulation terminate afterdischarges caused by cortical stimulation. *Neurology* 53: 2073–2081, 1999
18) Motamedi GK, Lesser RP, Miglioretti DL, et al.: Optimizing parameters for terminating cortical afterdischarges with pulse stimulation. *Epilepsia* 43: 836–846, 2002
19) Peters TE, Bhavaraju NC, Frei MG, Osorio I: Network system for automated seizure detection and contingent delivery of therapy. *J Clin Neurophysiol* 18: 545–549, 2001
20) Kossoff EH, Ritzl EK, Politsky JM, et al.: Effect of an external responsive neurostimulator on seizures and electrographic discharges during subdural electrode monitoring. *Epilepsia* 45: 1560–1567, 2004
21) Geller EB: Responsive neurostimulation: review of clinical trials and insights into focal epilepsy. *Epilepsy Behav* 88S: 11–20, 2018
22) Yamamoto T, Inaji M, Maehara T, Kawai K, Doyle WK: [(3)New therapeutic modalities using seizure detection devices for medically refractory epilepsy: AspireSR and the RNS System]. *No Shinkei Geka* 46: 247–262, 2018 (Japanese)
23) Ma BB, Rao VR: Responsive neurostimulation: candidates and considerations. *Epilepsy Behav* 88: 388–395, 2018
24) Jobst BC, Kapur R, Barkley GL, et al.: Brain-responsive neurostimulation in patients with medically intractable seizures arising from eloquent and other neocortical areas. *Epilepsia* 58: 1005–1014, 2017
25) Bergey GK, Morrell MJ, Mizrahi EM, et al.: Long-term treatment with responsive brain stimulation in adults with refractory partial seizures. *Neurology* 84: 810–817, 2015
26) Motamedi GK, Lesser RP, Miglioretti DL, et al.: Optimizing parameters for terminating cortical afterdischarges with pulse stimulation. *Epilepsia* 43: 836–846, 2002
27) Morrell MJ: RNS System in Epilepsy Study Group: responsive cortical stimulation for the treatment of medically intractable partial epilepsy. *Neurology* 77: 1295–1304, 2011

28) Sun FT, Morrell MJ: The RNS System: responsive cortical stimulation for the treatment of refractory partial epilepsy. *Expert Rev Med Devices* 11: 563–572, 2014
29) 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* 55: 432–441, 2014
30) Geller EB, Skarpaas TL, Gross RE, et al.: Brain-responsive neurostimulation in patients with medically intractable mesial temporal lobe epilepsy. *Epilepsia* 58: 994–1004, 2017
31) Lee B, Zubair MN, Marquez YD, et al.: A single-center experience with the NeuroPace RNS System: a review of techniques and potential problems. *World Neurosurg* 84: 719–726, 2015
32) Weber PB, Kapur R, Gwinn RP, Zimmerman RS, Courtney TA, Morrell MJ: Infection and erosion rates in trials of a cranially implanted neurostimulator do not increase with subsequent neurostimulator placements. *Stereotact Funct Neurosurg* 95: 325–329, 2017
33) Hirsch LJ, Mirro EA, Salanova V, et al.: Mesial temporal resection following long-term ambulatory intracranial EEG monitoring with a direct brain-responsive neurostimulation system. *Epilepsia* 61: 408–420, 2020
34) Devinsky O, Friedman D, Duckrow RB, et al.: Sudden unexpected death in epilepsy in patients treated with brain-responsive neurostimulation. *Epilepsia* 59: 555–561, 2018
35) Loring DW, Kapur R, Meador KJ, Morrell MJ: Differential neuropsychological outcomes following targeted responsive neurostimulation for partial-onset epilepsy. *Epilepsia* 56: 1836–1844, 2015
36) Meador KJ, Kapur R, Loring DW, Kanner AM, Morrell MJ: RNS® System Pivotal Trial Investigators: Quality of life and mood in patients with medically intractable epilepsy treated with targeted responsive neurostimulation. *Epilepsy Behav* 45: 242–247, 2015
37) DiLorenzo DJ, Mangubat EZ, Rossi MA, Byrne RW: 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, 2014
38) Kokoszka MA, Panov F, La Vega-Talbott M, McGoldrick PE, Wolf SM, Ghatan S: Treatment of medically refractory seizures with responsive neurostimulation: 2 pediatric cases. *J Neurosurg Pediatr* 21: 421–427, 2018
39) Singhal NS, Numis AL, Lee MB, et al.: Responsive neurostimulation for treatment of pediatric drug-resistant epilepsy. *Epilepsy Behav Case Rep* 10: 21–24, 2018
40) King-Stephens D, Mirro E, Weber PB, et al.: Lateralization of mesial temporal lobe epilepsy with chronic ambulatory electrocorticography. *Epilepsia* 56: 959–967, 2015
41) Quraishi IH, Mercier MR, Skarpaas TL, Hirsch LJ: Early detection rate changes from a brain-responsive neurostimulation system predict efficacy of newly added antiseizure drugs. *Epilepsia* 61: 138–148, 2020
42) Skarpaas TL, Tcheng TK, Morrell MJ: Clinical and electrocorticographic response to antiepileptic drugs in patients treated with responsive stimulation. *Epilepsy Behav* 83: 192–200, 2018

Corresponding author: Motoki Inaji, MD, PhD
Department of Neurosurgery, Tokyo Medical and Dental University, 1-5-45 Yushima, Bunkyo-ku, Tokyo 113-8519, Japan.
e-mail: inamnsrg@tmd.ac.jp