

# Intracranial Stimulation Therapy for Epilepsy

Tara L. Skarpaas\* and Martha J. Morrell\*<sup>†</sup>

\*NeuroPace, Inc., Mountain View, California 94043, <sup>†</sup>Department of Neurology, Stanford University Medical Center, Stanford 94043, California

**Summary:** Epilepsy is a common chronic neurological disorder effecting 1 to 2% of the population. Despite advances in anti-epileptic drug therapy, epilepsy surgery, and vagus nerve stimulation, approximately 30% of patients continue to have seizures. Intracranial stimulation is currently under investigation as an adjunctive treatment to anti-epileptic medications in adults with medically intractable epilepsy. Several different approaches are now being investigated. Specifically, acute and long-term clinical studies have delivered stimulation either to inhibitory regions outside the seizure focus or directly to the seizure focus. These studies have demonstrated the safety of intracranial stimulation and proof of principle in epilepsy patients. In addition to the different locations tested, clinical

studies have also used different temporal patterns of stimulation. The majority of studies have used open-loop or scheduled stimulation, in which, stimulation is delivered on a fixed schedule and is independent of electrographic activity. In contrast, a number of recent investigations have demonstrated the feasibility of closed-loop or responsive stimulation, which is stimulation that is contingent upon the detection of epileptiform activity.

This chapter will review the acute and long-term clinical studies of intracranial stimulation, including focal, and nonfocal, and open-loop and responsive stimulation. We will also discuss the optimization and safety of therapeutic parameters used in neurostimulation for epilepsy. **Key Words:** Epilepsy, responsive, neurostimulation, device, open-loop, closed-loop.

## INTRODUCTION

Approximately 2.5 million people in the United States have active epilepsy and 181,000 new cases of epilepsy are diagnosed each year. By 20 years of age, epilepsy has developed in 1% of the population, and by 75 years of age, the prevalence of epilepsy reaches 3%.<sup>1</sup> Despite advances in anti-epileptic drug (AED) therapy, epilepsy surgery, and vagus nerve stimulation (VNS), approximately 30% of patients continue to have seizures.<sup>2,3</sup> Thus, alternative treatment strategies are needed.

## ACUTE CLINICAL STUDIES

Intracranial stimulation is currently under investigation as an adjunctive treatment to anti-epileptic medications in adults with medically intractable epilepsy who are not candidates for potentially curative epilepsy surgery. As early as the 1950s, Penfield and Jasper<sup>4</sup> observed that cortical stimulation could disrupt epileptiform activity. Extinction was observed at the primary electrodes immediately after deliv-

ery of stimulation, after an afterdischarge, or after a spontaneous epileptic discharge, whereas suppression of normal and epileptiform activity was observed at distant sites and over large areas. Extinction was thought to represent post-excitatory depression and suppression to result from activation of inhibitory pathways, suggesting that stimulation at the seizure focus, as well as stimulation of inhibitory regions outside the focus could be used to inhibit epileptiform activity.

Subsequently a number of acute studies of both focal and nonfocal intracranial stimulation have been conducted, primarily in patients implanted with intracranial electrodes for purposes of localizing the seizure focus. In these studies, two main approaches to the timing of stimulus delivery have been explored, namely open-loop and closed-loop stimulation. Open-loop stimulation is delivered on a scheduled basis and is not contingent on the presence of epileptiform activity. In contrast, closed-loop (or responsive) stimulation provides stimulation only when abnormal (ictal or interictal) discharges are detected.

Kinoshita et al.,<sup>5,6</sup> in 2004 and 2005, respectively, tested the effect of focal open-loop cortical stimulation on interictal activity and electrocorticogram (ECoG) power spectra during extra-operative monitoring and functional mapping in a total of five patients with epilepsy of frontal lobe or mesial temporal lobe origin. The

Address correspondence and reprint requests to: Martha J. Morrell, M.D., Clinical Professor of Neurology, Stanford University, NeuroPace, Inc., 1375 Shorebird Way, Mountain View, CA 94043. E-mail: mmorrell@neuropace.com.

spike frequency and ECoG power spectra before and after high (50 Hz) and low (0.9 Hz) frequency stimulation were compared. There was a significant reduction in the number of interictal spikes post-stimulation compared with a pre-stimulation baseline. In addition, high frequency stimulation significantly decreased the power of low voltage fast activity. Other groups have also demonstrated a significant reduction in interictal spiking after open-loop stimulation of the hippocampus<sup>7,8</sup> and motor cortex.<sup>9</sup>

Kinoshita et al.,<sup>6</sup> 2005 also examined the effect on epileptiform activity of 50 Hz stimulation provided by cortical electrodes distant from the seizure focus (non-focal). This nonfocal stimulation did not inhibit spiking and did not alter the power of high-frequency activity. However, the regions stimulated in this study were different from nonfocal regions previously reported to have a suppressive effect on epileptic discharges. For instance, Zumsteg et al.,<sup>10</sup> 2006 demonstrated that open-loop stimulation of the anterior thalamic nucleus produced inhibition in the hippocampus. Moreover several studies have reported an effect of nonfocal stimulation on epileptiform activity and clinical seizures after stimulation of regions thought to be associated with the activation of inhibitory networks including the cerebellum,<sup>11</sup> caudate nucleus,<sup>12</sup> and several thalamic nuclei.<sup>13</sup>

A number of studies have also examined the effect of focal and nonfocal closed-loop stimulation on epileptiform activity in patients with subdural electrodes placed for pre-surgical evaluation. Lesser et al.,<sup>14</sup> 1999 examined the effect of cortical stimulation in 17 patients undergoing functional mapping for language, motor, and sensory regions. Afterdischarges produced by a localizing stimulus during the mapping could be aborted by a brief burst of stimulation delivered via the same electrodes used to elicit the afterdischarge. These results were extended by Motamedi et al.,<sup>15</sup> 2002 who demonstrated that the success of a brief burst to abort an afterdischarge was enhanced if the stimulus was applied early to the primary electrodes and at a specific phase of the afterdischarge.

Trials of closed-loop stimulation have been conducted in patients undergoing evaluation with intracranial electrodes as part of an epilepsy surgery evaluation. Peters et al.,<sup>16</sup> 2001 described a nonimplantable bedside prototype that included an ECoG acquisition system and computers that were used to store, process, and analyze ECoGs, and to control stimulation delivered through subdural electrodes by a Grass S12 stimulator (Grass Technologies, Warwick, RI). This system was used to deliver closed-loop stimulation in response to spontaneous seizures in eight patients.<sup>17</sup> Seizures originating from a discrete location received stimulation to the seizure onset zone. In contrast, seizures originating from multiple independent foci were treated with stimulating electrodes implanted in the anterior thalamic nucleus. All patients received high fre-

quency (100–500 Hz) biphasic stimulation. Closed-loop stimulation reduced the seizure rate by 55.5% in the focal group and 40.8% in the nonfocal group. This study demonstrated that automated closed-loop, high-frequency stimulation could be delivered in close temporal proximity to the seizure onset and suggested that closed-loop stimulation might produce a significant reduction in clinical seizures.

Results from a small subset of patients enrolled in a large multi-center acute study of a second bedside prototype also suggested that closed-loop stimulation could alter or block electrographic seizures.<sup>18</sup> The external responsive neurostimulator (eRNS) is a battery-operated device that processes digital data in real-time and has three different detection tools that can be programmed to identify a patient's electrographic seizure onset.<sup>18</sup> The authors reported that responsive stimulation terminated some electrographic seizures. Figure 1 shows examples of electrographic seizures in one patient (FIG. 1A) without and (FIG. 1C) with closed-loop stimulation. Note the return to baseline electrographic activity after stimulation in Figure 1C.

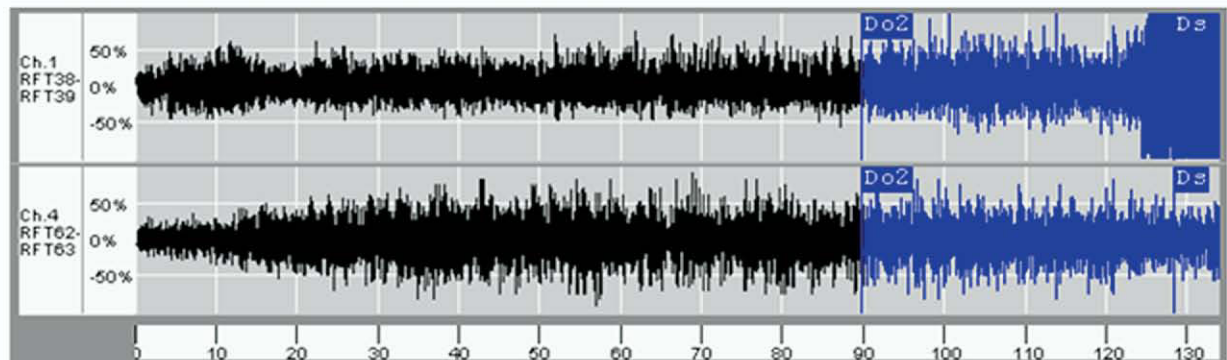
These acute studies suggest that both focal and nonfocal stimulation can acutely inhibit epileptiform activity and that both open-loop and closed-loop stimulation can be effective. However, the acute studies do not address the effect of stimulation on clinical seizures, nor do they address the efficacy or safety of long-term intracranial stimulation.

## CHRONIC CLINICAL STUDIES AND IMPLANTABLE DEVICES

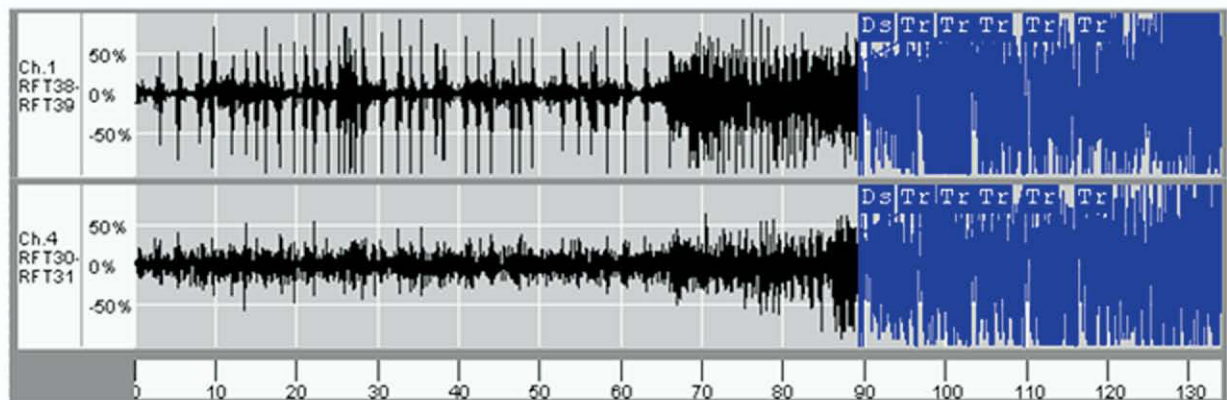
The first long-term clinical studies of chronic brain stimulation provided open-loop cerebellar stimulation and reported a significant reduction in clinical and electrographic seizures.<sup>11</sup> However, subsequent randomized trials did not show benefit.<sup>19</sup> Other studies of brain stimulation in persons with medically uncontrolled epilepsy have shown a reduction in seizure frequency after stimulation of regions outside the seizure focus including several thalamic nuclei, subthalamic nucleus, caudate, mammillary bodies, locus coeruleus, and basal ganglia. Most results indicate that indirect stimulation can more successfully inhibit secondarily generalized seizures than complex partial seizures.<sup>20</sup>

To date, a number of small clinical studies have tested the efficacy of implantable devices that deliver stimulation to the seizure onset zone. Many of these studies have focused on open-loop stimulation to mesial temporal structures. Velasco et al.,<sup>8</sup> 2000 treated patients implanted with hippocampal depth leads (placed via an occipital approach) with high-frequency biphasic stimulation. Clinical seizures and interictal spikes were blocked with 130 Hz, 200 to 400  $\mu$ A, stimulation. This stimulation produced no histopathological tissue damage and no negative effect on short-term memory. In addi-

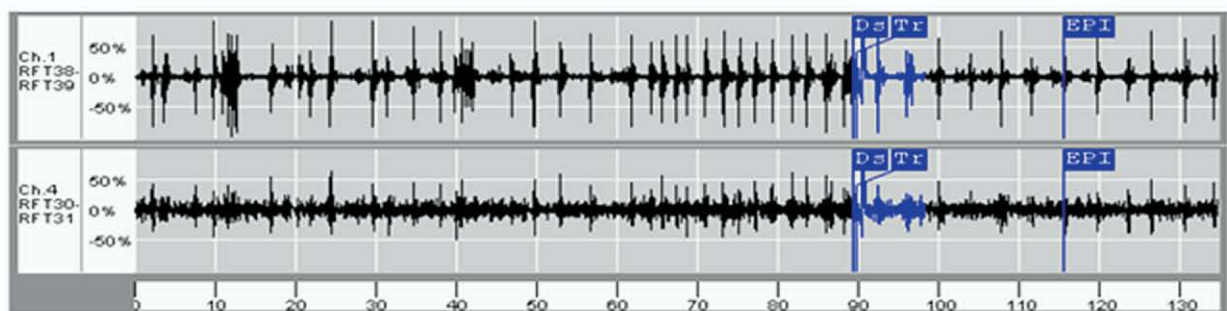
## A Stored ECoG Record from eRNS



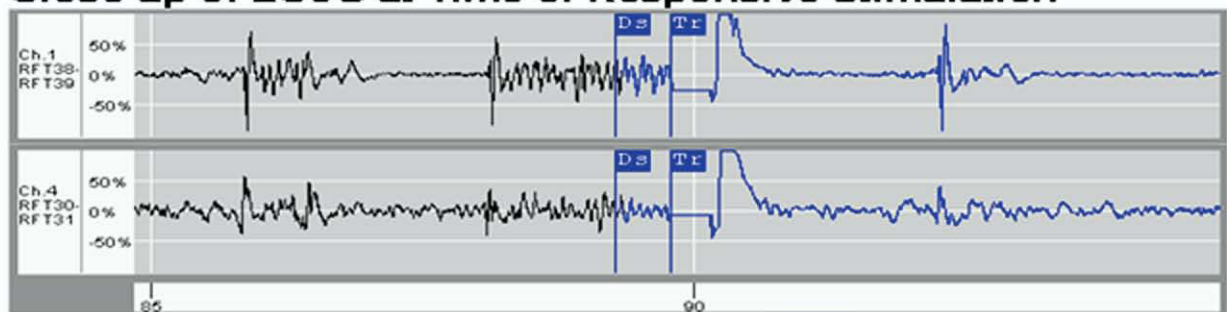
## B



## C



## Close-up of ECoG at Time of Responsive Stimulation



**FIG. 1.** Electrographic (ECoG) recordings of electrographic seizures from the same patient. (A) Seizure recorded without stimulation. The electrographic activity correlated with a clinically reported seizure. Detection, denoted by blue, had not been tuned for the seizure onset and was late. (B) Seizure recorded with focal high-frequency stimulation delivered by the eRNS late after the seizure onset. Stimulation is denoted by Tr. Again detection had not been tuned for the seizure onset and thus detection and stimulation were late and the seizure progressed. (C) Early detection of electrographic seizure onset pattern and early focal responsive high-frequency stimulation delivered to the seizure onset by the eRNS. FFT = fast Fourier transform.

tion, they noted that stimulation therapy was most effective when the electrodes extended to the anterior pes hippocampus near the amygdala. A subsequent study followed patients for 5 to 21 months after implantation of amygdala hippocampal depth leads and a pulse generator.<sup>21</sup> They noted a >50% reduction in seizure frequency in 4 of 7 patients, one of whom was seizure free for 1.5 years. In addition, 2 of the patients could be tapered off of one AED. No side effects related to the stimulation were reported. Although one randomized trial of hippocampal stimulation demonstrated a smaller nonsignificant seizure reduction,<sup>22</sup> a recent double-blind trial in 9 patients demonstrated a significant reduction of seizure frequency in response to hippocampal stimulation.<sup>23</sup> Importantly, there were no adverse effects reported in either study and the stimulation did not have any detrimental effects on cognitive and memory functions.

Focal stimulation of neocortical onsets has also been used to treat intractable seizures. One patient had a seizure focus in the primary motor hand region.<sup>9</sup> During functional brain mapping, it was noted that direct 50 Hz stimulation for 3 minutes at 2 mV significantly suppressed interictal spiking for 10 minutes. The spiking then gradually returned but could be suppressed with subsequent stimulation. The patient was implanted with a permanently indwelling electrode array at the seizure focus and a pulse generator was placed in the subclavicular area. The patient received cyclical open-loop stimulation (biphasic 50 Hz, 2.1 mV for 3 min on, 10 min off) for 5 years without evidence of injury. Moreover, the stimulation reduced the seizure frequency by more than 90%.

The first implantable responsive neurostimulator for epilepsy, the NeuroPace RNS System (NeuroPace, Inc., Mountain View, CA), is currently being evaluated for safety and efficacy in clinical trials for the treatment of intractable partial onset epilepsy in adults. A schematic of the implanted device appears in Figure 2. The implantable components include a cranially implanted neurostimulator that is connected to up to two depth and/or strip leads containing four electrodes each. An external programmer is used by the physician to program detection and stimulation parameters and retrieve stored electrographic activity. A wand allows wireless communication between the stimulator and the programmer. A data transmitter is provided to the patient to allow uploading and remote monitoring of device data between clinic visits. The RNS System continually analyzes the patient's electrographic activity and automatically delivers electrical stimulation to the seizure focus when the patient's characteristic epileptiform activity is detected. An initial single-center report demonstrated a 45% decrease in seizures in 7 of 8 patients with a mean follow-up of 9 months.<sup>24</sup> A randomized, double-blind, sham-controlled pivotal clinical trial is currently being conducted to demonstrate the safety and efficacy of the RNS System.



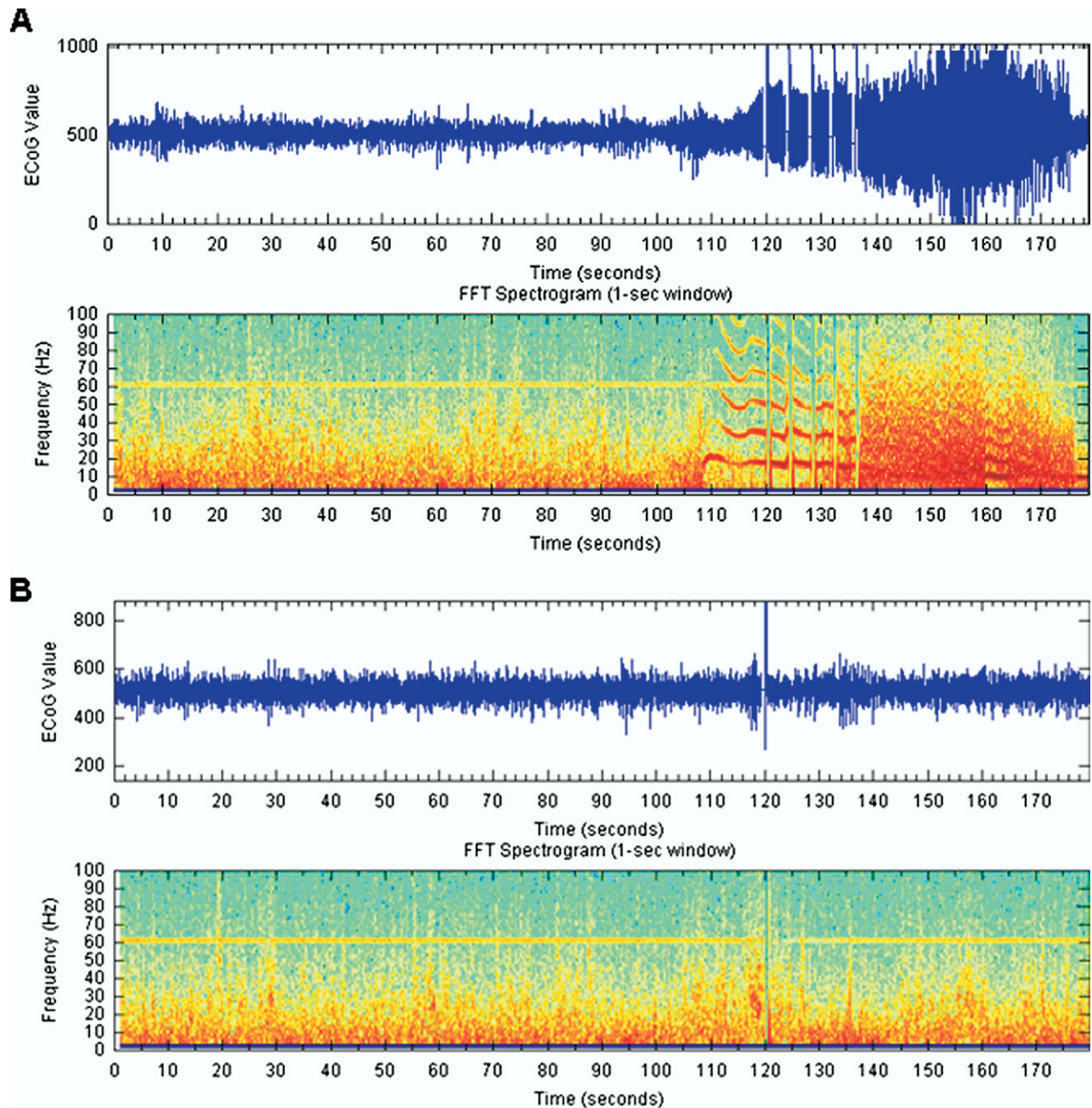
FIG. 2. Schematic of the NeuroPace RNS neurostimulator, depth and strip leads. Inset shows RNS neurostimulator.

### OPTIMIZING THERAPEUTIC STIMULUS PARAMETERS

A variety of parameters may influence the response to both open- and closed-loop stimulation. These parameters include dose or number of stimulations, stimulus frequency, current intensity, stimulus duration, stimulus waveform, and the location. Both high and low frequencies have been shown to inhibit epileptiform activity and seizures, and the optimal stimulus frequency may depend on the region being stimulated.<sup>12</sup> In addition, the efficacy of responsive stimulation may be influenced by how early the electrographic seizure can be detected. For instance, stimulations delivered later in the seizure failed to terminate the electrographic event, whereas stimulations delivered early resulted in a return to baseline activity (FIG. 3). Thus adjusting detection parameters to detect at the earliest sign of an electrographic event may also be important in optimizing responsive stimulation.

### Safety of intracranial stimulation

No damage has been observed in human cortex exposed to intermittent stimulation used to perform functional mapping as long as the charge delivered remains below 50 to 60  $\mu\text{C}/\text{cm}^2/\text{phase}$ .<sup>25,26</sup> However, there is a safety concern that chronic subthreshold stimulation, such as that used by implantable devices for the treatment of epilepsy, may induce neural injury. Experience with deep brain stimulation for Parkinson's disease suggests that long-term continuous stimulation can be delivered safely.<sup>27</sup> Animal studies have suggested that tissue damage due to stimulation is correlated with charge density per phase, and the total charge per phase, as well as with cumulative exposure of tissue to stimulation.<sup>28</sup> Intermittent stimulation provides less cumulative expo-



**FIG. 3.** Time series and spectrograms of electrographic seizures receiving (A) late stimulation and (B) early stimulation relative to the seizure onset using the implantable RNS System. Note that (A) the seizure continues to evolve when focal stimulation is delivered several seconds after the onset of the seizure, whereas (B) the electrographic activity does not evolve when focal stimulation is delivered earlier.

sure than continuous stimulation. Further studies are required to determine if either open- or closed-loop stimulation produces damage to tissue after long-term use.

Surgically implanting devices to deliver intracranial stimulation for the treatment of epilepsy may be associated with some additional risks. Reports from the implantation of deep brain stimulators for Parkinson's disease, pain, and hearing loss suggest that the procedure is associated with a 5% risk of infection and a 5 to 7.5% risk of intracerebral hemorrhage.<sup>20</sup> Surgical risks may

vary depending on the site of implantation, the size of the device, and the general health of the patient population.

## SUMMARY

Implantable neurostimulation devices may provide a new therapy for medically intractable epilepsy patients. One advantage of intracranial stimulation for the treatment of epilepsy is that the therapy is largely reversible. In addition, stimulation therapy can be delivered to a

specific onset region or inhibitory network and can be adjusted for individual patients. Thus, intracranial stimulation may offer more specificity than anti-epileptic drugs. Ongoing clinical trials of intracranial stimulation may reveal that there is more than one approach to brain stimulation that is safe and effective. Further studies will be required to identify patients who might benefit from stimulation, to identify safe and effective stimulation targets and ascertain the optimal stimulation parameters for individuals or groups of patients.

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