Chronic unlimited recording electrocorticography–guided resective epilepsy surgery: technology-enabled enhanced fidelity in seizure focus localization with improved surgical efficacy

Clinical article

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Object. Epilepsy surgery is at the cusp of a transformation due to the convergence of advancements in multiple technologies. Emerging neuromodulatory therapies offer the promise of functionally correcting neural instability and obviating the need for resective or ablative surgery in select cases. Chronic implanted neurological monitoring technology, delivered as part of a neuromodulatory therapeutic device or as a stand-alone monitoring system, offers the potential to monitor patients chronically in their normal ambulatory setting with outpatient medication regimens. This overcomes significant temporal limitations, pharmacological perturbations, and infection risks inherent in the present technology comprising subacute percutaneous inpatient monitoring of presurgical candidates in an epilepsy monitoring unit.

Methods. As part of the pivotal study for the NeuroPace Responsive Neurostimulation (RNS) System, the authors assessed the efficacy of the RNS System to control seizures in a group of patients with medically refractory epilepsy. Prior to RNS System implantation, these patients were not candidates for further resective surgery because they had temporal lobe epilepsy with bilateral temporal sources, frontal lobe reflex epilepsy with involvement of primary motor cortex, and occipital lobe epilepsy with substantial involvement of eloquent visual cortex. Without interfering with and beyond the scope of the therapeutic aspect of the RNS System study, the authors were able to monitor seizure and epileptiform activity from chronically implanted subdural and depth electrodes in these patients, and, in doing so, they were able to more accurately localize the seizure source. In 5 of these study patients, in whom the RNS System was not effective, the notion of resective surgery was revisited and considered in light of the additional information gleaned from the chronic intracranial recordings obtained from various permutations of electrodes monitoring sources in the frontal, temporal, parietal, and occipital lobes.

Results. Through long-term analysis of chronic unlimited recording electrocorticography (CURE) from chronically implanted electrodes, the authors were able to further refine seizure source localization and sufficiently increase the expected likelihood of seizure control to the extent that 4 patients who had previously been considered not to be candidates for surgery did undergo resective surgery, and all have achieved seizure freedom. A fifth patient, who had a double-band heterotopia, underwent surgery but did not achieve significant seizure reduction.

Conclusions. Chronic unlimited recording electrocorticography–guided resective epilepsy surgery employs new monitoring technology in a novel way, which in this small series was felt to improve seizure localization and consequently the potential efficacy of resective surgery. This suggests that the CURE modality could improve outcomes in patients who undergo resective surgery, and it may expand the set of patients in whom resective surgery may be expected to be efficacious and therefore the potential number of patients who may achieve seizure freedom. The authors report 4 cases of patients in which this technique and technology had a direct role in guiding surgery that provided seizure freedom and that suggest this new approach warrants further study to characterize its value in presurgical evaluation. Clinical trial no.: NCT00572195 (ClinicalTrials.gov).

Key Words • intracranial monitoring • subdural electrodes • epilepsy surgery • intracranial electrodes • seizure focus localization • chronic monitoring

Abbreviations used in this paper: AED = antiepileptic drug; CURE = chronic unlimited recording electrocorticography; ECoG = electrocorticographic; EEG = electroencephalography; IPG = implantable pulse generator; MEG = magnetoencephalography; RNS = Responsive Neurostimulation; RUMC = Rush University Medical Center; SISCOM = subtraction ictal SPECT coregistered to MRI; VNS = vagus nerve stimulation.

The irreversible nature of resective epilepsy surgery imposes a barrier to its acceptance despite its potential to provide seizure freedom; consequently, substantial unmet need is driving innovations along 2

This article contains some figures that are displayed in color online but in black-and-white in the print edition.
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pathways: 1) development of reversible neuromodulatory technologies and 2) refinement in presurgical patient assessment and seizure circuit source localization.

Technological advancements in noninvasive multimodality functional imaging, such as subtraction ictal SPECT coregistered to MRI (SISCOM), magnetoencephalography (MEG), and PET, aid in both patient selection and in preoperative planning.14 New chronically implanted neural monitoring technologies, such as those developed by NeuroPace6,10 and separately by NeuroVista2,3,5 enable evaluation of an entirely new modality of pre-resective identification of the ictal circuit, that is, chronic unlimited recording electrocorticography (CURE)–guided resection.

The NeuroPace Responsive Neurostimulation (RNS) System delivers contingent electrical stimulation to a seizure focus and has recently been assessed in a multicenter pivotal clinical trial.9 Distinct from this intended function, we have used its monitoring capability to assess the utility of the chronic unlimited recording electrocorticography (CURE) modality in the planning of resective surgery.

Among patients with epilepsy, approximately 60% achieve good seizure control. In the remaining cases, the seizures are refractory to medical therapy and the patients are potential candidates for surgical therapy. Presurgical evaluation and surgery are performed, respectively, to identify and resect the epileptogenic zone, defined as the smallest region of cortex that, when resected, results in seizure freedom.12 Noninvasive presurgical evaluation, including structural imaging with MRI, functional imaging with SISCOM, PET, and MEG, and electroencephalographic monitoring using scalp electroencephalography (EEG) recordings, when concordant, is sufficient for anatomical focus localization and surgical planning. In a fraction of these, approximately 25%, invasive monitoring is required to determine the location of the ictal source or epileptic circuit with sufficient accuracy.11,15 Subacute intracranial monitoring, first described in the late 1930s by Penfield,10 using subdural and cortical depth electrocorticography, offers the potential to record extracellularly from populations of neurons orders of magnitude smaller than the populations accessed via scalp EEG,6,19 which requires a surface area greater than 10 cm² to generate detectable signals.17 Subacute invasive monitoring, restricted by infection risk to typical durations of 5–10 days and maximum durations of 2–4 weeks, remains severely limited in the time domain and in the ability to capture seizures.9 In temporal lobe epilepsy, the most common subtype, reduction of antiepileptic drug (AED) dosage levels is usually required to induce a seizure within this time frame;6 however, acutely lowering AED dosage levels may make seizures generalize more rapidly, making localization more difficult.

For a minority of patients undergoing subacute invasive electrocorticographic (ECoG) monitoring, the invasive data are insufficient for localization and surgical planning, and these comprise 2 groups: 1) those in whom it is immediately clear that the seizure has not been satisfactorily localized and who undergo subdural strip and/or grid removal and do not proceed to resective surgery and 2) those in whom the ictal onset area appears to have been localized and who undergo resective surgery but do not realize significant reduction in seizure frequency or magnitude. Chronic unlimited recording electrocorticography (CURE) may benefit both of these groups as well as patients in whom localization confidence is less than 100%. Furthermore, postresection CURE may be valuable for confirmation of efficacy and for guiding further resection if required. This research was performed in patients previously enrolled in the NeuroPace RNS System Pivotal trial (NCT 00572195).

Methods

Patients with epilepsy who were not candidates for resective surgery but who did meet the inclusion criteria for the RNS System pivotal clinical trial were offered the opportunity to enroll in the study. Objectives, risks, expectations, surgical procedure, perioperative care, and long-term management were discussed in detail.6 Enrollment was voluntary in all cases. For those patients wishing to enroll, written informed consent was obtained. The protocol and the multicenter RNS System pivotal clinical trial were both approved by the Rush University Medical Center (RUMC) institutional review board.

The inclusion criteria for the NeuroPace RNS System pivotal trial were as follows: 1) disabling motor simple partial seizures, complex partial seizures, or secondarily generalized seizures; 2) failure of a minimum of 2 AEDs; 3) an average of 3 or more seizures every 28 days for 3 consecutive 28-day periods; 4) age between 18 and 70 years; and 5) no more than 2 epileptogenic regions (NeuroPace, Inc., confidential investigational plan).

In patients with mesial temporal epileptic sources, the temporal depth electrodes were placed in perihippocampal white matter to interface with tracts presumed to be involved in seizure generation or propagation.13 Beyond and without impacting the therapeutic aspect of this study, ECoG signals were recorded and analyzed. For patients in whom the RNS System was not efficacious and whose seizures remained refractory, further analysis of these recordings enabled us to better characterize and localize epileptogenic sources.

Results

Five of 11 patients implanted with the RNS System during the NeuroPace feasibility study and pivotal clinical trial at RUMC were considered for cortical resective surgery, in part, guided by the implanted RNS System ECoG monitoring system. In 4 patients, a high degree of confidence in source localization was realized, and these patients subsequently underwent resection and achieved a very significant reduction in their seizure frequency following CURE-guided resection.

The patient in Case 1, a right-handed 26-year-old woman, had initially refused to consider further resective surgery at the time of her RNS System implantation because of complications of previous surgery. She subsequently underwent CURE-guided right temporal lobec-
tomy and as of this writing has been seizure free for 31 months. The patient in Case 2, a right-handed 29-year-old man with bilateral temporal epileptic sources, was not considered a candidate for resective surgery at the time of RNS System implantation at age 21. He was subsequently found to have a resectable left temporal focus and has been seizure free for 53 months since CURE-guided surgery consisting of a left temporal corticectomy for traumatic cortical scar seizure focus resection at age 25. The patient in Case 3, a 45-year-old man with multiple seizure types beginning at age 14, had undergone multiple subpial transections and vagus nerve stimulation (VNS) system placement and removal, and was considered not to be a surgical candidate. He underwent RNS System implantation at age 37 with strip electrodes in the interhemispheric fissure and right superior frontal gyrus with revision to a depth electrode in the right superior frontal gyrus and subsequently underwent CURE-guided resective surgery at age 42. He has since remained seizure free for 41 months. The patient in Case 4, a 42-year-old right-handed man with a history of seizure disorder since age 8, had undergone a left occipital multiple subpial transection procedure at age 28 with transient relief of seizures; a left occipital cortical focus resection and subpial transection procedure 10 months later, also at the age of 28; and further resection comprising basal-occipital and basal-temporal resection at age 34. He subsequently underwent CURE-guided resective surgery consisting of an occipital disconnection procedure at age 36. He had one postoperative seizure during medication taper and has since remained seizure free for 69 months.

In the fifth patient, who had a double-band heterotopia, 2 sources were identified, but others beyond those two were suspected; he was felt to have a lower likelihood of postresection improvement, elected to proceed with resection at another institution, and did not realize a significant improvement in seizure control after resection. In all 4 of the patients in whom CURE monitoring provided source localization in which we felt confident that good seizure control was likely, excellent control or seizure freedom was achieved. Prior to CURE monitoring, each was either felt not to be a candidate for or refused further resective surgery and was enrolled in the RNS trial. These 4 cases are described in detail below. Data from these cases are summarized in Table 1.

Case 1

**History.** This right-handed female patient was diagnosed with a Grade 1 right temporal astrocytoma at age 13 months and underwent right craniotomy at another institution for debulking 3 times (at ages 14 months, 3 years, and 5 years) resulting in resection of most of the right middle temporal gyrus and accompanied by radiation therapy, with residual left-sided weakness and hyperreflexia. At age 13, she began experiencing seizure-like symptoms, including staring spells with an alteration in awareness as well as independent prolonged episodes of nausea and vomiting; at age 17, she was diagnosed with epilepsy. She was thought to have 2 types of seizures, described as staring spells and head shaking. Her staring spells occurred 1 or 2 times per week, lasted about 1 minute, and were characterized by chewing movements, drooling, or reaching for invisible objects with her hands. The head-shaking episodes were characterized by head movements in a lateral turning (“no-no”) direction and were accompanied by nausea, vomiting, and dizziness, lasting up to several hours.

A vagus nerve stimulator was implanted when the patient was 17 years old (in 2004). It did not improve her seizures and was removed 3 years later when the RNS System was implanted (see below).

An MRI study at age 19 (April 2006) demonstrated encephalomalacia and gliosis of the superior right temporal lobe, consistent with previous resection (see Fig. 1A[i]). Video EEG with bilateral sphenoidal electrodes revealed right inferior temporal runs of prolonged right perisylvian rhythmic delta range activity correlated with her nausea and vomiting. In June 2006, further video EEG monitoring demonstrated bilateral interictal epileptiform discharges. SPECT at baseline demonstrated no lesions, and PET demonstrated absent and reduced metabolism in the right temporal lobe, consistent with encephalomalacia. Follow-up MRI in February 2007 showed no change (Fig. 1A[iii]). Because of her complications from previous resective surgery at another institution, the patient would not consider further resective surgery; however, she was eligible for the RNS System trial.

**Implantation of RNS System and Postoperative Course.** At age 20 (in July 2007), she underwent RNS System implantation with lead placements comprising implantation of a left occipitotemporal depth electrode and reopening of right craniotomy with implantation of right temporal lobe subdural electrodes. Postoperative CT confirmed placement (Fig. 1A[iii]).

Approximately 3 years after implantation of the RNS System, she was not satisfied with a 50% reduction in seizure frequency. These seizures were characterized by a feeling of nausea or dizziness without head shaking (at age 24). During this admission, video EEG monitoring revealed focal sharp waves and focal slowing in the right temporal region, and episodes of nausea and head shaking were captured. SISCOM and video EEG activity were concordant, consistent with a localization-related epilepsies throughout the right temporal lobe. Novel subtracted activated SPECT employing RNS System stimulation with functional imaging to assess projection from the stimulation sites, without triggering a seizure, demonstrated connectivity between the left temporal region (stimulated RNS System leads) and the right anterior temporal and left occipital areas (Fig. 1B[iii]). This was shown with pre-RNS System SISCOM (April 2006), which demonstrated right superior temporal activity correlated with episodes of emesis (Fig. 1B[i]).

Chronic ECoG data obtained from the RNS System from July 2007 to November 2010 enabled further characterization of her epileptiform activity. Persisting refractory epileptiform activity was recorded from the distal contacts (Channels 1 and 2) of her right temporal subdural electrodes (Fig. 1C). Seizure activity related to her left temporal focus was well controlled with the left
<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yrs),†</th>
<th>Sex</th>
<th>Epilepsy Dx &amp; Features</th>
<th>Epilepsy Dx Etiology/Foci</th>
<th>Semiology</th>
<th>EEG</th>
<th>Sx Correlates</th>
<th>Modality</th>
<th>Multifocal or Eloquent</th>
<th>Ictal SPECT</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>26, F</td>
<td>C</td>
<td>complex partial Sz</td>
<td>rt temp Gr I astrocytoma</td>
<td>1) severe nausea &amp; vomiting &amp; head shaking; 2) staring spells</td>
<td>1) rt inf temp runs of prolonged rt perisylvian rhythmical delta range activity</td>
<td>Phase I (scalp standard) only</td>
<td>bilat interictal epileptiform discharges</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>29, M</td>
<td>M</td>
<td>complex partial &amp; secondarily generalized tonic-clonic Sz</td>
<td>1) rt temp primary; 2) Lt temp post-traumatic</td>
<td>1) aura (“feels weird” or “going to pass out”) followed by silence &amp; automatisms triggered by music or stress</td>
<td>rt ant temp epileptic Sz, Lt temp lobe epileptic Sz, rt frontal epileptic Sz</td>
<td>Phase I scalp (75 channel) (Phase II at outside hospital)</td>
<td>bilat temp epileptic sources</td>
<td>rt sup temp hyper-perfusion; slight Lt parietal, BG, cerebellar</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>45, M</td>
<td>M</td>
<td>reflex epilepsy</td>
<td>primary sensory area in rt mesial frontoparietal region s/p multi subpial resections</td>
<td>sudden loss of muscle tone w/ falls triggered by somatosensory stimulation of Lt foot (i.e., walking on uneven or textured surfaces)</td>
<td>ictal pattern at vertex correlated w/ stepping up on a stool</td>
<td>Phase II</td>
<td>single eloquent focus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>42, M</td>
<td>F</td>
<td>simple partial Sz, progressed to also include complex partial Sz</td>
<td>left occip cortical focus</td>
<td>seeing colors in rt visual field followed by loss of vision on that side, progressing to images of a cartoon train, later developing automatisms</td>
<td>1) epileptiform discharges in the Lt occip region w/ secondary generalization; 2) rare epileptiform discharges in Lt temp region</td>
<td>Phase II</td>
<td>2 suspected eloquent foci (Lt occip &amp; rare Lt temp)</td>
<td>intense ictal perfusion in sup &amp; lat portion of Lt temp lobe</td>
<td></td>
</tr>
</tbody>
</table>

* Ant = anterior; b/c = because; BG = basal ganglia; Dx = diagnosis; Gr = Grade; inf = inferior; interhem = interhemispheric; multi = multiple; occip = occipital; s/p = status post; subseq = subsequent; sup = superior; Sz = seizure(s); temp = temporal.

† Patient ages refer to the age at the most recent assessment.
TABLE 1: Summary of 4 cases in which CURE-guided surgery led to seizure freedom* (continued)

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Prior Resective Surgery</th>
<th>Other Interventions</th>
<th>Reason for Lack of Surgical Candidacy</th>
<th>CURE Monitoring, Insights, &amp; Interventions</th>
<th>Surgical Intervention</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Gr I rt temp astrocytoma s/p resection ×3</td>
<td>initially refused further resection b/c of homonymous hemianopsia &amp; hemiparesis following initial resection at outside hospital</td>
<td>rt temp subdural &amp; lt occip-temp depth</td>
<td>rt temp source refractory; lt temp controlled</td>
<td>further resection of rt temp lobe &amp; hippocampus remnant</td>
<td>Sz freedom (31 mos)</td>
</tr>
<tr>
<td>2</td>
<td>bilat temp epileptic sources</td>
<td></td>
<td>rt temp depth &amp; lt temp subdural (×2, lat &amp; basal); subseq repositioning of lt temp lat electrode</td>
<td>lt temp source refractory; rt temp source controlled</td>
<td>lt temp corticectomy for traumatic cortical scar Sz focus resection</td>
<td>Sz freedom (53 mos)</td>
</tr>
<tr>
<td>3</td>
<td>VNS (failed)</td>
<td>suspected involvement of eloquent sensorimotor cortex</td>
<td>rt sup frontal subdural &amp; interhem fissure by central sulcus; subseq revision of rt frontal to depth</td>
<td>localization of source to focal region on medial frontal surface</td>
<td>resection of focal region of rt medial frontal lobe</td>
<td>Sz freedom (41 mos)</td>
</tr>
<tr>
<td>4</td>
<td>1) subpial transection, 2) lt occip resection &amp; subpial transection, 3) lt basal-occip resection &amp; lt basal-temp resection</td>
<td>VNS implanted &amp; removed ×2</td>
<td>certainty of rt homonymous hemianopsia w/ uncertainty of cure due to uncertain localization w/ possible involvement of eloquent lt temp structures</td>
<td>lt mesial occip interhem fissure subdural, lt temp depth (in white matter adjacent to hippocampus)</td>
<td>localization of source to single source in the lt occip region; gave confidence that focus was single</td>
<td>lt occip lobe disconnection procedure</td>
</tr>
</tbody>
</table>

* Ant = anterior; b/c = because; BG = basal ganglia; Dx = diagnosis; Gr = Grade; inf = inferior; interhem = interhemispheric; occip = occipital; s/p = status post; subseq = subsequent; sup = superior; Sz = seizure(s); temp = temporal.
† Patient ages refer to the age at the most recent assessment.
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temporal depth electrode. These insights, which were gained beyond the subacute inpatient implanted monitoring sessions, suggested increasing seizure activity on the right and decreasing activity on the left. Based upon this information, it was determined that further right-sided resection may provide improved seizure control.

**CURE Surgery and Outcome.** In November 2010 (at age 23), the patient underwent a reopening and expansion of the previous right temporal craniotomy for right temporal lobe and hippocampus remnant resection, with removal of the superior temporal gyrus, uncus, and hippocampus posteriorly to the level of the tectal plate. The RNS System subdural electrode was then repositioned on the cut edge of the temporal stem. Postoperative CT (November 2010) confirmed resection and demonstrated repositioning of the right subdural electrode (Fig. 1A[iv]).

As of this writing the patient has been seizure free since the CURE surgery (31 months).

**Case 2**

**History.** This right-handed male patient had his first seizure at age 17 after being stung by a jellyfish. This first seizure was followed by the development of complex partial and secondarily generalized tonic-clonic seizures. The findings of an MRI study performed in 2000 were normal. Two years later, the patient was struck in the left side of the head with a shot (heavy spherical object used in shot-put competition) at a track meet, sustaining a left posterior temporal fracture with traumatic brain injury, contusion, and subdural hematoma resulting in worsening of his seizures.

His typical complex partial seizures were characterized by an aura in which he reported feeling “weird” or as if he was “going to pass out,” followed by silence and automatisms in the form of staring, smiling, chewing movements, speech arrest, drooling, and coughing, followed by

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**Fig. 1. Case 1.** A: Anatomical imaging: i) Axial T1-weighted, sagittal T1-weighted, and coronal T2-weighted MR images obtained in April 2006 (before implantation of the RNS system after initial right temporal glioma resection). ii) Follow-up coronal hippocampal FLAIR (upper) and axial T1-weighted (lower) MR images obtained in February 2007. iii) Lateral scout (upper) and axial (lower) CT images obtained in November 2007 after RNS System implantation. iv) Lateral scout (upper) and axial (lower) CT images obtained in November 2010 after CURE-guided surgery. B: Functional imaging: i) SISCOM from April 2006 (pre-RNS) demonstrates right superior temporal ictal activity, which was observed in association with episodes of emesis (in contrast with her left-sided seizures, which were associated with staring episodes). ii) Novel subtracted activated SPECT images obtained in November 2010 (before CURE-guided surgery) reveals connectivity between the left temporal region (stimulated RNS leads) and right anterior temporal and left occipital areas. C: Chronic ECoG recording demonstrating epileptiform activity in the distal contacts (Channels 1 and 2) of the right temporal subdural electrode.
head turning. His seizures occurred once per week, and auras occurred 4 to 5 times per week, often triggered by listening to music with ear buds or by stress. The complex partial seizures were occasionally accompanied by generalization.

An MRI study performed in August 2003 (when the patient was 20 years old) demonstrated encephalomalacia with hyperintense T2 and hypointense T1 signal in the lateral left temporal lobe, consistent with the presence of old blood products, with normal hippocampal formations and temporal horns (Fig. 2A[i]). SISCOM demonstrated hyperperfusion in the right superior mesial temporal lobes and the remainder of the cerebrum (Fig. 2B[i]). Video EEG with bilateral sphenoidal electrodes captured numerous seizures and revealed primarily left temporal lobe epileptic activity. Video EEG performed 2 months later with bilateral sphenoidal electrodes captured 5 seizures of right anterior temporal lobe onset. These, being contra-

lateral to the patient’s previously documented left temporal seizure focus, established bilateral temporal epileptic sources. When the patient was 21 years old, video EEG with bilateral sphenoidal electrodes again demonstrated bitemporal foci. Preoperative SISCOM demonstrated an ictal focal increase in perfusion in the superior aspect of the right temporal lobe, consistent with a seizure focus in this region. An MRI study performed in June 2004 showed no change from the 2003 study.

Because of his bitemporal seizure foci, the patient was not considered to be a surgical candidate for definitive or palliative resection, but he did meet inclusion criteria for the RNS System pivotal clinical trial.

**Implantation of RNS System and Postoperative Course.** At age 21 (in June 2004), he underwent implantation of a skull-based RNS System with 3 electrode arrays, comprising: 1) a 4-contact depth electrode in the right parahippocampal white matter (this electrode}
was implanted stereotactically, 2) a 4-contact subdural electrode strip in the left basal temporal region, and 3) a 4-contact subdural electrode strip along the left lateral temporal region. Postoperative CT confirmed positioning of the electrodes (Fig. 2A[iii]). Two of these electrode arrays were connected at initial implantation, and one was placed for future potential use. Postoperative RNS System recordings demonstrated abnormal activity at both the right and left intracranial electrodes.

The patient derived improvement in the right temporal seizures but had poor control of the left temporal seizures, realizing about a 50% reduction in clinical seizures overall.

Functional imaging using subtracted activated SPECT performed 1 year following RNS System implantation (July 2005) demonstrated in the left inferior temporal lobe a small area of reduced perfusion unchanged between ictal and interictal studies and on the right a slight change in perfusion between ictal and interictal studies, consistent with the patient’s known right temporal seizure focus.

Revision of RNS System. Two years later, at age 23, during surgery to change the RNS System implantable pulse generator (IPG), the contact arrangement of the left temporal subdural electrodes was also changed in an attempt to attain better control over the left temporal seizures.

Resection of Seizure Focus. Chronic ECoG data obtained from the RNS System from August 2006 to August 2008 demonstrated persisting clinical and electrographic seizures originating from a left temporal focus (Fig. 2C), confirming both that the left temporal focus was the source of his disabling seizures and that the seizures arising from the right temporal region were controlled with the RNS System. This provided some reassurance of the potential therapeutic benefit of left temporal resective surgery.

In August 2008 (when the patient was 25 years old), 4 years after initial RNS System implantation and 2 years after the left electrode configuration change, the decision was made to perform an awake left temporal seizure focus resection, because of his persisting seizures arising from the left temporal region of encephalomalacia as evidenced by CURE monitoring, and to leave the RNS System in place. The presurgical confirmatory workup, also in August 2008 included a SISCOM (Fig. 2B[i]) and high-density scalp EEG monitoring with 75 scalp electrodes and dipole scalp source modeling (Fig. 2B[ii]). Both were concordant with a right temporal focus, and this was resected.

Awake cortical mapping demonstrated expressive speech impairment at 8 mA applied superior to the lateral temporal subdural electrodes but no language impairment with stimulation near the electrodes. A corticectomy was performed, resulting in the removal solely of scarred, firm, and avascular-appearing brain tissue with no normal-appearing brain being removed. Intraoperative recording demonstrated improvement in the ECoG signal on the left. The left lateral temporal subdural electrode was then repositioned to be immediately behind the line of resection and was secured by suturing to the dura. The repositioned left lateral temporal electrode and the right depth electrode were then reattached to the RNS IPG: The left subtemporal electrode was left in place (see Fig. 2A[iii]).

Outcome. On postresection follow-up the patient denies having had any seizures, with the last seizure being one that occurred 2.5 months prior to CURE-guided surgery. As of this writing, he has been seizure free for 23 months.

Case 3

History. This male patient had his first seizure at age 14 (1981). At that time, his seizures manifested as complex partial seizures. At age 27, he developed simple partial seizures in the form of a reflex epilepsy characterized by sudden loss of muscle tone and falls triggered by somatosensory stimulation, particularly of his left foot, including walking on uneven or textured surfaces, upon being startled, by going down stairs or escalators, descending in an elevator, or by exposure to strong winds. These were not typically accompanied by loss of consciousness but did occasionally result in secondary generalization with tonic-clonic seizures. At age 33 (2000), he underwent implantation of a VNS system with little benefit.

An MRI study performed when the patient was 35 years old (June 2002) demonstrated normal anatomy with a slightly smaller hippocampus on the right (Fig. 3A[i]), and he underwent Phase 2 monitoring with two 4-contact double-sided subdural electrode strips in the interhemispheric space and a 32-channel grid on the right convexity. His seizures were localized to the primary sensory area in the right mesial frontoparietal region. The subdural electrodes were removed, a multiple subpial transection procedure was performed, and the VNS IPG was removed, leaving the lead in place. He realized brief relief from seizures, but the seizures subsequently returned.

Nine months later, video EEG again demonstrated reflex epilepsy, characterized by tonic posturing and falling backward, triggered by stepping on a stool and correlated with an ictal pattern at the vertex. His MRI findings were unchanged.

Implantation of RNS System and Postoperative Course. At age 37, he underwent right frontal craniotomy for implantation of an RNS System with two strip electrodes, including a 4-contact electrode placed in the interhemispheric space at approximately the interhemispheric projection of the central sulcus and a second 4-contact electrode along the posterior portion of the superior frontal gyrus. Postoperative CT demonstrated placement (Fig. 3A[iii]). Seizures with falls persisted, and 10 months later, he underwent video EEG, which again demonstrated reflex epilepsy, with epileptic spikes elicited by being startled and by jerking of his lower extremity.

Revision of RNS System and Postoperative Course. Seizures with falls persisted, approximately twice per week, and at age 40, he underwent replacement of the RNS System IPG and reconnection to the interhemispheric electrode and to a new depth electrode placed in
the right superior frontal gyrus, as shown on postoperative CT (Fig. 3A[iii]). Seizures nonetheless persisted.

Chronic ECoG data obtained from the RNS System from August 2004 to January 2010 enabled further characterization of his epileptiform activity. Recordings from the interhemispheric subdural electrode demonstrated brief reflex seizures, consistent with the vertex EEG activity recorded on video EEG, most prominent on the second electrode (Channel 2) and which spontaneously terminated after a very short interval (Fig. 3B). Insights gained beyond the subacute inpatient implanted monitoring sessions confirmed the interhemispheric focus as the source of his reflex seizures. Based upon these data, it was determined that resection of this focus could potentially be curative.

Resection of Seizure Focus. Presurgical video EEG confirmed focal epilepsy arising from a right mesial frontoparietal origin, and the patient underwent awake right craniotomy with removal of the RNS System and resection of the seizure focus, as shown on postoperative CT (Fig. 3A[iv]) at age 42 (in 2010). The interhemispheric electrode was used to guide the resection, which began in the right medial premotor region and was extended laterally with cortical mapping and under ECoG guidance until epileptiform discharges had ceased. The patient developed expected intraoperative left shoulder weakness and left lower-extremity weakness, more pronounced distally.

Outcome. Postoperatively, the patient had left shoulder abduction weakness (3/4) and left leg monoplegia (0/5). By the time of discharge, he had partial improvement of his left leg strength proximally (hip to 2/5) and persisting distal left leg weakness (elsewhere 0/5), requiring the use of an ankle-foot orthosis. He was discharged to an acute rehabilitation facility, where his condition continued to improve.

At 1-month postoperative follow-up, the patient denied having had any seizures since surgery; but he had experienced multiple falls, which he attributed to mechanical left leg weakness. Follow up video EEG monitoring demonstrated no seizures. On subsequent follow-up the patient denied having had any seizures, with the last seizure being in January 2010, about 1 month prior to his CURE-guided surgery. As of this writing, he has been seizure free for 41 months, and his most recent full examination (at age 45, in August 2012) showed continued improvement in motor strength in the left upper extremity (5/5 throughout) and left lower extremity (4/5 proximal and 3/5 distal).

Case 4

History. This right-handed male patient began to experience seizures at 8 years of age. Initially, they mani-
fested as formed images of a cartoon train in his right visual field, lasting 20 seconds and occurring 1–2 times per week. These seizures subsequently progressed to include visual blackouts, obscuring part of the train. When he was 14–15 years of age, the seizures further progressed to become complex partial seizures in which he was unable to see at all, experienced automatisms, and was unaware of his surroundings. At age 24 (in March 1995), he underwent implantation of a VNS system as part of the VNS pivotal trial; the system was removed 6 months later.

By age 27, his seizures consisted of colored lights in the right visual field followed by complex partial seizures with lip smacking and hand movements, lasting 30–40 seconds and occurring approximately 18 times per month. He also began experiencing occasional secondary generalizations.

At age 28, he underwent left temporal occipital craniotomy for subdural electrode placement, with a strip and grid over the left occipital pole. The seizure focus was localized to the left occipital lobe involving the interhemispheric fissure and the suboccipital region with additional epileptiform activity in the left anterotemporal region, felt to be secondary to spread from the occipital region. The electrodes were removed, and multiple subpial transections were performed under ECoG guidance in the low occipital lobe and extending to the posterior temporal lobe.

He remained seizure free for 3 months, and then his seizures returned. A year later, he underwent repeat monitoring via 4 subdural electrode arrays, placed subtemporally, at the temporoparietal junction, suboccipitally, and in the interhemispheric fissure, and an epidural grid overlying and avoiding the vein of Labbé. Monitoring for 10 days suggested a focus in the suboccipital region. Electrodes were removed, and he underwent resection of the left suboccipital cortical seizure focus, with ECoG improvement after each resection but persistence of epileptiform spiking activity. Multiple subpial resections were then performed, and significant resolution of interictal discharge was observed. He remained seizure free for 11 months, and then seizures returned. The seizure frequency increased to up to 40 seizures per month. The seizures involved an aura with a red to blue color in the right upper visual field accompanied by images of a train with a smoking chimney.

At age 29, video EEG monitoring with sphenoidal electrodes demonstrated one complex partial seizure felt to have originated from the left suboccipital region. Three months later, he underwent left occipital craniotomy with placement of 3 subdural electrodes in the suboccipital plane, an epidural grid in the occipital region, and an epidural cylinder. After monitoring for a week, his seizure focus was felt to be too generalized and to involve important structures in his left temporal lobe such that surgery was not recommended.

At age 31 (in October 2001), the patient underwent implantation of a new VNS system (his second), with placement of a new triple-helical vagal nerve electrode proximal to the scarred-down previously implanted vagus nerve segment. His seizures changed such that they began to occur as transient visual images, which clustered, up to 20 in 2 hours. After 8 months, monitoring with sphenoidal electrodes demonstrated frequent sharp waves and focal slowing in the left temporal lobe. The VNS system was considered to be ineffective and was removed 8 months after implantation. Magnetic resonance imaging revealed unchanged slight prominence of the left temporal horn (Fig. 4A[i]).

The patient’s seizure frequency increased to 50 seizures per month and the seizure characteristics changed, manifesting as an aura of colors in the right visual field followed by loss of vision and confusion with lip smacking and arm movements. At age 32, intracranial monitoring with bilateral sphenoidal electrodes demonstrated these focal seizures as well as secondarily generalized seizures with epileptiform discharges in the left posterior quadrant and rarely in the left temporal region. SPECT imaging demonstrated an areas of intense ictal perfusion in 1) the superior and lateral portion of the left temporal lobe and 2) the left caudate region and adjacent left temporal and parietal areas. SISCOM demonstrated 2 regions of ictal activity in the left mesial occipital and left basolateral temporal regions (Fig. 4B[i] and [ii], respectively). Two months later, the patient underwent a left temporal occipital craniotomy with placement of 4 subdural electrode arrays in the suboccipital region (Fig. 4A[iii]). Monitoring for 1 week revealed epileptiform activity and 1 generalized tonic-clonic seizure localized to the left temporal occipital areas. A basal-occipital resection and a basal-temporal resection were performed (Fig. 4A[iii]), with significant improvement in postresection electrocorticography. His right visual field auras changed from a “soul train” to a “spark” postoperatively.

Implantation of RNS System and Postoperative Course. The patient’s seizures persisted, and at age 34 he underwent a left occipital craniotomy with implantation of an RNS System with subdural and depth electrodes. A subdural electrode strip was placed in the interhemispheric fissure in contact with the left mesial occipital region, and a depth electrode was placed in the temporal lobe white matter parallel to the hippocampus, as demonstrated on postoperative CT (Fig. 4A[iv]). Ictal and baseline SPECT imaging (February 2006) demonstrated the surgical absence of portions of the left occipital and adjacent temporal lobes and no focal area of increased perfusion.

Recordings from the occipital electrode are shown in Fig. 4C. Ictal activity was not recorded, but propagation of high-frequency stimulation signals are recorded in the left occipital subdural recording leads in response to the repetitive bipolar stimulation of left posterior mesial temporal white matter depth contacts. Propagation to ipsilateral primary visual cortex was also observed by semiology and blood flow measures. The correlation of the aura semiology with that elicited by the stimulation of the left posterior mesial temporal white matter depth contacts suggested involvement in the same circuit.

Chronic ECoG data obtained from the RNS System from October 2004 to August 2006 enabled further characterization of the patient’s epileptiform activity. Initially, the seizures were thought to be possibly due to dual pathology; however, chronic recordings from the RNS
System provided reassurance that the focus was single. Furthermore, activity was well localized to the calcarine sulcus, and stimulation reproduced the aura. Based upon these findings and the consequent increased confidence in a therapeutically effective resection, the certainty of hemianopsia was ultimately accepted by the patient in exchange for a chance for seizure freedom, and the decision was made to undertake resective surgery.

The RNS System was ineffective for the patient after only a transient initial improvement of several months, and 22 months later, when the patient was 35 years old, the RNS System was removed (Fig. 4A[v]). His seizures persisted, occurring 30–50 times per month, often in one or two clusters of 20–40 seizures each; the majority were brief complex-partial seizures without preceding visual auras.

North Carolina Medicaid declined to cover further surgical procedures out of state at our institution, and the patient’s care was transferred to Duke University in November 2006. Monitoring with EEG showed 5 typical complex partial seizures without visual aura originating from the left occipital region.

**Disconnection Surgery and Outcome.** At age 36, the patient underwent a frameless stereotactically guided left occipital lobe disconnection procedure (April 2007), with significant improvement in his seizure control. As of this writing (April 2013), he had experienced only 1 post-resection seizure (in September 2007 during a trial of phenobarbital tapering) and since then has been free of seizures for 69 months.

**Discussion**

In each of these 4 cases, diagnostic localization or certainty thereof was insufficient for either the patient...
or the treating physicians to proceed with resective surgery. In this small set of patients, chronic intracranial monitoring facilitated refinement of source localization beyond that realized with subacute in-hospital intracranial recordings, and this provided the treating neurology and neurosurgery teams with sufficient confidence in the realization of a satisfactory probability of a curative outcome to proceed with resective surgery. Before chronic unlimited recording electrocorticography (CURE)-guided surgery, in all 4 cases, the patients’ quality of life was severely compromised by frequent and refractory seizures; following surgery, a prolonged seizure-free state was achieved.

As shown in Table 1, the spectrum of available technologies was employed in the initial pre-CURE workup, including Phase I, Phase I with high-resolution (75 channel) scalp electrodes, and Phase II invasive monitoring. For each of these modalities and cases, additional valuable information gleaned from the CURE monitoring provided source localization insights that were helpful and ultimately successful in guiding resective surgery and providing seizure-free states for patients with previously refractory seizures. This is a preliminary study that demonstrates the experience at one center using one device (NeuroPace RNS System). The NeuroPace RNS System has since received FDA approval (November 14, 2013) during the final revision of this manuscript. Further, the RNS System records a series of time epochs of data rather than truly continuous data; as such, this particular system is not truly “unlimited” in the acquisition of data but provides some proof of concept of the utility of a continuous monitoring system. A similar experience was found in a first-in-man study using another device under development (NeuroVista Seizure Advisory System), which does provide truly continuous recordings, and there are other chronically implanted monitoring systems under development that may also be found to provide similar utility. One limitation of the CURE modality, as evaluated using the RNS System platform, is the absence of simultaneous video recording data, which is valuable in corroborating clinical seizures. Other implementations of the CURE modality, such as might be performed with the NeuroVista Seizure Advisory System, could make use of simultaneous auditory data, which is useful in confirming clinical seizure activity. Future implementations could also include video or other sensory data, which may confirm or refute the presence of concomitant clinical seizure activity during periods of detected or suspected electrographic seizures.

This study underscores the known limitations of subacute in-hospital intracranial monitoring, our present standard of care, and demonstrates in a small set of initial patients the potential value and utility of a new modality, that of chronically implanted unlimited recording of electrocorticography, in augmenting the safety and efficacy of resective surgery.

Conclusions

Because of the irreversible nature of resective surgery, a high preoperative certainty in source localization is required to mitigate and justify the potential risks. When noninvasive imaging and neurophysiological modalities are not concordant, we are at present left with a suboptimal invasive (Phase 2 epilepsy monitoring unit) study, which is time limited, environmentally constrained, and often pharmacologically perturbed from ambulatory baseline, as our arbiter for use in deciding whether to offer potentially curative surgery. We demonstrate in a small series of patients that a fully implanted chronic ambulatory recording system, such as the device used here or as could be readily used with another implanted monitoring system, offers the potential to substantially advance the standard of care in resective surgery and thereby expand the potential set of patients who may realize seizure freedom.

As a small case series, this is admittedly a preliminary study. Further funding, development, and clinical testing of such technologies offers promise to aid in the precision and in the efficacy of resective and neuromodulatory therapy for patients with epilepsy. From our limited experience to date, CURE-guided resection offers the potential to provide efficacious resective surgery to a carefully selected subset of patients who otherwise may not be considered candidates for resective surgery.

Disclosure

Dr. DiLorenzo is the founder of NeuroVista (acquired by Cyberonics) and has an ownership interest in intellectual property relating to chronic neural monitoring and to closed-loop neuromodulation. The RNS System was provided by NeuroPace as part of their pivotal trial. The design, objectives, methods, and analyses constituting the present study were independent of the NeuroPace pivotal trial and required no specific financial support.

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