Epilepsy & Behavior xxx (2009) xxx–xxx

Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

Advances in the Application of Technology to Epilepsy: The CIMIT/NIO Epilepsy Innovation Summit ☆

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ARTICLE INFO

Article history:
Received 15 June 2009
Accepted 20 June 2009
Available online xxxx

Keywords:
Epilepsy
Engineering
Technology
Treatment
Electroencephalography
Neuroimaging
Brain function

ABSTRACT

In 2008, a group of clinicians, scientists, engineers, and industry representatives met to discuss advances in the application of engineering technologies to the diagnosis and treatment of patients with epilepsy. The presentations also provided a guide for further technological development, specifically in the evaluation of patients for epilepsy surgery, seizure onset detection and seizure prediction, intracranial treatment systems, and extracranial treatment systems. This article summarizes the discussions and demonstrates that cross-disciplinary interactions can catalyze collaborations between physicians and engineers to address and solve many of the pressing unmet needs in epilepsy.

Introduction

The engineering sciences are being increasingly applied to problems in the diagnosis and treatment of patients with epilepsy. In 2008, a meeting sponsored by the Center for the Integration of Medicine and Innovative Technology (CIMIT; www.cimit.org) in Boston and the Neurotechnology Industry Organization (NIO; www.neurotechindustry.org) brought together more than 75 clinicians, scientists, engineers, and industry representatives to discuss these advances and to provide a roadmap for further development in four general areas: evaluation for epilepsy surgery, seizure onset detection and seizure prediction, intracranial treatment systems, and extracranial treatment systems.

The power of blending the medical arts and applied sciences often starts with convening experts from across a range of disciplines and providing opportunities for social networking. This meeting report summarizes the presentations and illustrates how cross-disciplinary interactions are critical for the establishment of collaborations between physicians and engineers to address and solve many of the pressing unmet needs in epilepsy.

1. Evaluation for epilepsy surgery

1.1. Overview

Donald L. Schomer

When anticonvulsants fail to control seizures in a patient with epilepsy or if medical therapy is associated with disabling or unacceptable side effects, the physician considers alternative treatments, one of which is excisional brain surgery. The goal of such an approach is to cure the patient by removing only the minimal amount of brain tissue necessary to render the patient free from their seizures with little to no additional neurological deficit.

Historically, planning for excisional surgery started with a careful review of the patient's history and performance of a detailed neurological exam. Importantly, the history needed to demonstrate that the seizure semiology (description of the onset and progression of the seizure with particular emphasis on the likely relevant neuroanatomy) has been consistent over time and the presumed location for seizure onset is an area that can be approached surgically without causing long-term problems. It is also essential to

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doi:10.1016/j.yebeh.2009.06.028

Please cite this article in press as: Schachter SC et al. Advances in the Application of Technology to Epilepsy: The CIMIT/NIO Epilepsy Innovation Summit Epilepsy Behav (2009), doi:10.1016/j.yebeh.2009.06.028

demonstrate medical refractoriness or the presence of untenable side effects from medications.

The workup for the patient was then directed to demonstrating the focal electrical onset of seizures. This was accomplished by recording electroencephalograms (EEGs), using either scalp-based or intracranial electrodes, and, often, reducing or stopping seizure drugs while the patient was monitored in a hospital-based EEG facility. Additionally, the workup included some measure of brain imaging, either with computed tomography (CT) or magnetic resonance (MR) scans, to look for an anatomically based "lesion" and determine its correlation to the clinical exam, history, and EEG findings. Testing for cognitive dysfunction also was essential and often accompanied by an intracarotid amytal test (IAT or Wada study) to corroborate hemispheric lateralization for speech and memory.

Over the last 10–15 years, there have been a number of significant advances in virtually all aspects of this classic presurgical evaluation. Magnetoencephalography has become more widely available and offers significantly better spatial resolution than electroencephalography without any loss of temporal resolution. MR imaging (MRI) has added functional imaging capabilities that allow us to demonstrate the anatomical locations of different cerebral functions as well as interictal epileptic discharges by imaging the blood flow changes associated with them. With new MRI acquisition sequences, we can image white matter pathways and extend our imaging abilities in ways that we are only beginning to comprehend. Coupling MRI with the infusion of magnetically susceptible nanoparticles appears to even further improve our abilities to image functional regions of the brain and to better define epileptic regions. MR spectroscopy has now been able to give us smaller and smaller voxels, which allows us to study the biochemical makeup of areas that may assist with surgical planning, an advance made possible by higher-field-strength MR machines. Older technology has been modernized and subsequently become more readily available for use. Such is the example of single-photon-emission computed tomography (SPECT) scanning. As technology develops, machines are reduced in size and can be placed near the inpatient recording unit, for example, in conjunction with recently designed and tested isotopes. Such devices make recording interictal, ictal, and postictal blood flow patterns much easier and allow us to demonstrate ictal zones, interictal abnormalities, and the areas of the brain affected by a seizure. We are also able to image augmented or deficient receptor densities and relate such findings to the electrical or anatomical findings. Improvements in computer-based algorithms have given us better localization of normal and abnormal neurological activity and do so close to "real time."

These advances are discussed next by those who are pushing the frontiers of neurological investigation and changing how we think about the presurgical evaluation of patients with medically intractable focal onset epilepsy.

1.2. Use of magnetoencephalography to localize seizure onset

Gregory L. Barkley

Magnetoencephalography (MEG) measures the magnetic fields produced by current flow within the brain and has been demonstrated to be of value in assessing seizure onset in patients with intractable focal epilepsy under evaluation for epilepsy surgery. Anatomical imaging studies such as MRI and CT identify static structural lesions but do not provide information on seizure onset, as structural lesions may or may not be associated with epilepsy. MEG, like EEG, provides conclusive proof of epileptic seizures by displaying well-recognized patterns of paroxysmal discharges that evolve over milliseconds to minutes. No other technology can demonstrate the millimeter localization accuracy and millisecond time sensitivity of MEG except intracranial EEG (ECoG), and EcoG can only do this when the intracranial electrodes are placed within a few millimeters of the epileptic source (for review, see [1]). In contrast, MEG studies provide this information painlessly and noninvasively in an outpatient setting.

MEG signals arise primarily from intracellular current flow in pyramidal neurons known as primary currents. EEG signals arise primarily from extracellular current flow known as secondary currents. Pyramidal neurons in sulci are oriented such that current flows are tangential to the scalp and produce detectable magnetic fields. In contrast, active neurons on gyral surfaces produce little or no measurable external magnetic fields but their radial currents contribute to EEG. MEG signals are extremely weak, and recordings are performed within a shielded room to minimize environmental artifacts.

Unlike EEG, magnetic fields are not affected by intervening tissues. This makes modeling of MEG sources, sometimes called magnetic source imaging (MSI), easier because spherical headshape models can be used with MEG with greater accuracy than when the same models are applied to EEG. The most commonly used source modeling in MEG is the single equivalent dipole. This is not a physical point but rather can be thought of as the "center of gravity" of a collection of synchronously active neurons. This modeling works best for stationary nondistributed sources and is accurate for modeling many epileptic spikes. Descriptions of newer techniques of advanced modeling used in our laboratory, including MR-FOCUSS, coherence mapping, and beamformer techniques, can be found on our web page, www.megimaging.com.

A number of studies have analyzed the contribution of the MEG-defined irritative zone to surgical outcome in epilepsy. Wheless et al. [2] found that MEG was second only to ictal intracranial video/EEG for predicting the epileptogenic zone in patients with excellent surgical outcome. Mamelak et al. [3] showed that MEG was highly correlated with the zone of seizure origin identified by ECoG when more than five spikes clustered on MEG. Stefan and colleagues [4] reported that MEG spikes were detected in 70% of presurgical candidates, with the correct lobe predicted in 89%. This rate was higher for extratemporal foci than temporal foci. MEG provided additional information not found in other modalities in 35% of their series and unique information in 10% of their patients. Assaf et al. [5] showed that MEG patterns predicted intracranial source localization and surgery outcome in temporal lobe epilepsy. Knowlton and colleagues [6] reported that the positive predictive value for seizure localization with MEG was 82–90%, depending on whether computed against intracranial EEG alone or in combination with surgical outcome.

In 2007, we retrospectively reviewed all patients who had MEG prior to epilepsy surgery [7]. Seventy-five patients with Engel Class I or II outcome with at least 2 years postsurgical follow-up were analyzed. MEG data were compared with surgical site and classified according to their contribution. MEG provided unique localizing information in 15% of patients and supplemental information that improved localization in 13%, whereas discordant information was found in only 4%. This information was most helpful in patients with neocortical epilepsy.

Recent articles document the unique contributions of MEG to the prospective evaluation of patients undergoing epilepsy surgery [8–10]. Sutherling et al. evaluated MEG in surgery decision making in neocortical epilepsy and found that MEG added nonredundant information in 33% of 69 presurgical patients, provided beneficial information in 21% of those who had undergone surgery, and changed the surgical treatment in 9% [10]. Knowlton et al. performed a similar analysis in 62 patients who completed epilepsy surgery out of 160 patients whose seizures were not sufficiently localized by noninvasive studies [8,9].

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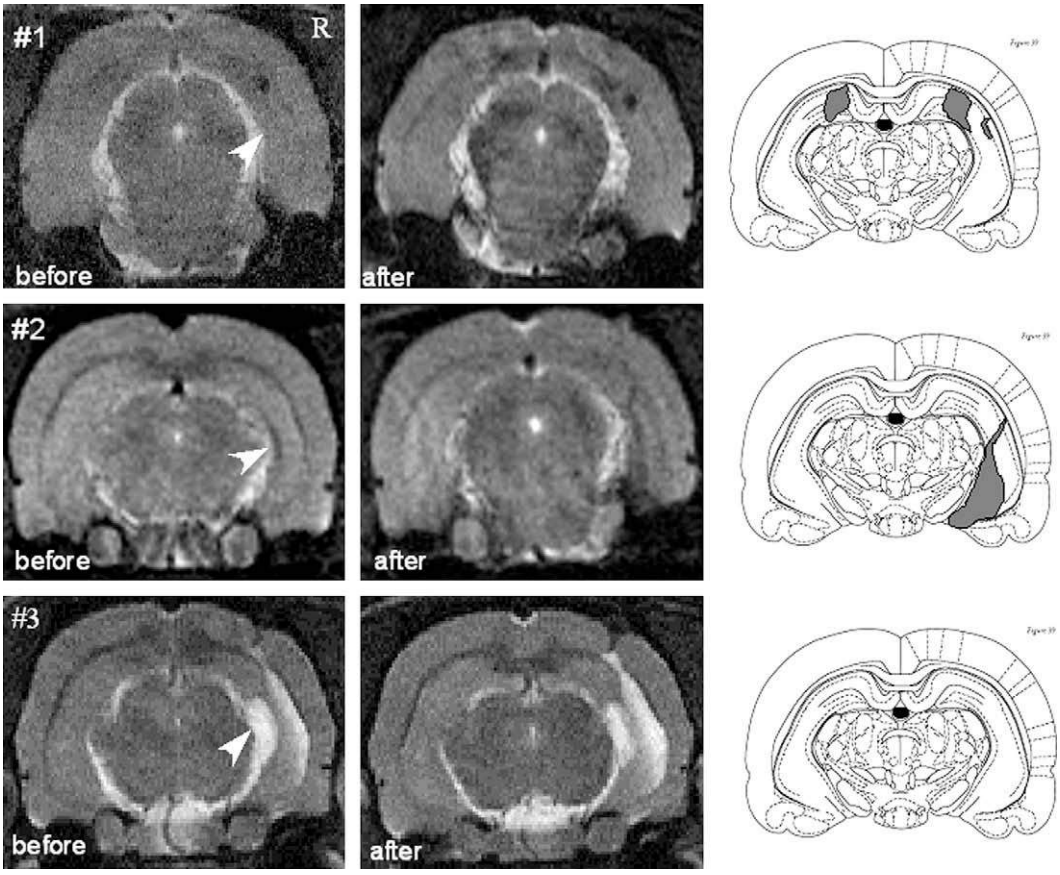

Fig. 1. MR images of rats #1, 2, and 3 (top to bottom) are shown before (left column) and after (middle column) tail vein injection of AMT-MNPs (3.7 mg Fe/kg). Rat #1 showed bilateral uptake of particles, rat #2 showed unilateral uptake, and rat #3 did not show any particle uptake. Arrows in the left column show the areas of hippocampal atrophy due to kainic acid injection. Rats #1 and 2 had spontaneous behavioral seizures; rat #3 did not show any behavioral seizure activity. The location of areas with AMT-MNP uptake is shown in the right column on sections from Paxinos [1]. Images were taken 6 h after AMT-MNP injection for rats #1 & 3, and 4 #h after injection for rat 2.

They found that MEG studies did not detect spikes in 13 of 62 patients, which can be equated in effort, utility, and cost to a day of inpatient video/EEG monitoring when no spikes or seizures are detected. For the 49 patients with positive MEG information, the sensitivity for Engel Class I outcome was 72%, the specificity was 70%, the positive predictive value was 78%, and the negative predictive value was 64%. They noted that a MEG study early in the surgery evaluation showing multifocal or generalized epileptic discharges had a high predictive value of poor outcome and was sufficient to stop further evaluation. MEG yield was greatest in lateral temporal lobe onset epilepsy and next highest in other neocortical onset epilepsies. MEG, 5-fluorodeoxyglucose positron emission tomography (FDG-PET), and ictal SPECT were complementary with only partial redundancy, and each was found to be an independent predictor of seizure-free outcome.

MEG is also useful in the noninvasive evaluation of eloquent cortex. Grover et al. [11] reported that MEG visual hemifield mapping altered the surgical approach and changed the outcome in about 15% of the patients in their series of operated patients with parieto-occipital brain tumors. Therefore, combining MEG mapping of eloquent cortex with epileptic spike mapping can lead to decisions to avoid epilepsy surgery because of anticipated morbidity when the epileptic focus and eloquent cortex overlap. In addition, in patients with tumors, MEG mapping of eloquent cortex may lead to decisions to proceed with either a resection or a biopsy depending on the anatomic relationship of the eloquent cortex to the lesion.

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1.3. Covalently conjugated magnetonanoparticles in epilepsy

Massoud Akhtari, Jerome Engel, Jr.

We have developed nonradioactive and targeted magnetonanoparticles (MNPs) capable of crossing the blood–brain barrier (BBB) and of concentrating in the epileptogenic tissues of acute and chronic animal models of temporal lobe epilepsy (TLE) to render these tissues visible on magnetic resonance imaging (MRI). Nonradioactive á-methyl tryptophan (AMT) was covalently attached to MNPs composed of iron oxide and dextran. A rodent model of TLE was prepared by injecting kainic acid into the right hippocampus. AMT-MNPs were injected in the tail vein of these animals during the chronic stage of epilepsy. MRI scans were obtained before and after particle injection in all animals, and intracranial EEGs were obtained after completion of MRI studies. AMT-MNPs crossed the BBB, and intraparenchymal uptake was visible on MRI (Fig. 1). In the chronic condition, AMT-MNP uptake correlated with the occurrence of spontaneous seizures, and the location of uptake appeared to agree with bilateral or unilateral epileptogenicity as confirmed by a subsequent intracranial EEG (Fig. 2).

In conclusion, nonradioactive AMT-MNPs can cross the BBB and may accurately localize epileptogenic cerebral regions. The MNP–MRI approach is potentially applicable to the use of any bioactive molecules as ligands for imaging normal and abnormal localized cerebral functions accurately, safely, and inexpensively.

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1.4. Localizing EEG abnormalities using neuroimaging

Francis McGlone, Ross Dunseath

Recent advances in the development of neuroimaging techniques capable of combining electroencephalographic and functional MRI (fMRI) data in real time enable the localization of areas of increased blood flow associated with specific EEG events, and are being applied to presurgical mapping and localization of epileptogenic zones in pharmacoresistant focal epilepsy [1,2]. The traditional approach to removing the two main sources of induced noise—(1) scanner induced, for example, radiofrequency (rf) and switching gradient magnetic fields, and (2) ballistocardiogram effects—have relied on postprocessing software techniques and various matched template subtraction algorithms. The main pro-

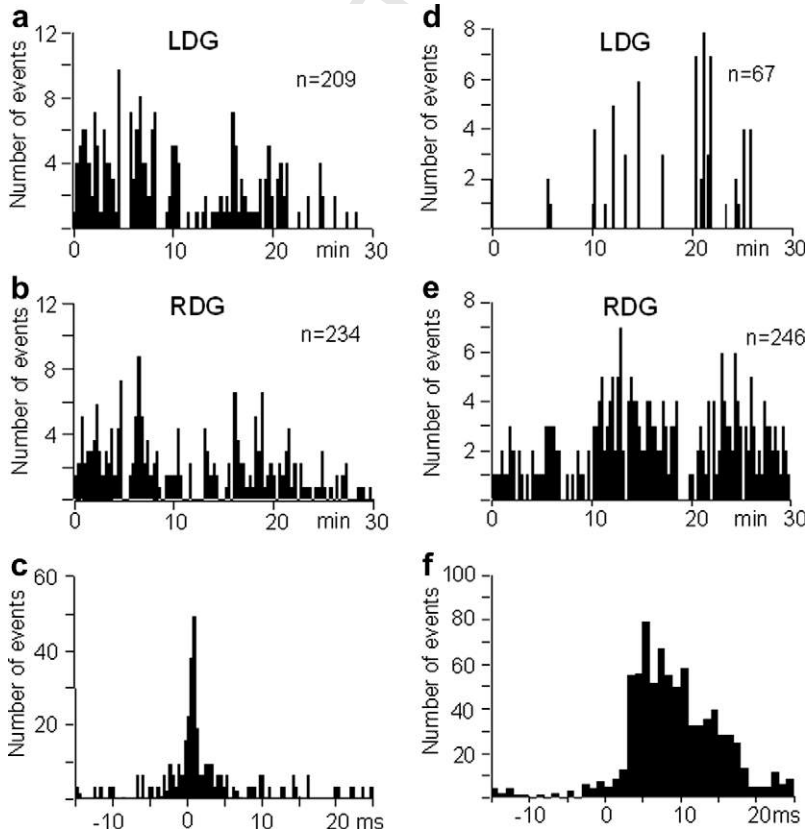

Fig. 2. Left: Rate of interictal spikes in rat 1 with bilateral AMT-MNP uptake recorded during 30 min of immobility and slow wave sleep in the left (a) and right (b) dentate gyrus; (c) peri-event histogram of interictal spikes recorded in the left dentate gyrus versus right dentate gyrus. The rate of interictal spikes was the same on both sides. Right: rate histogram of interictal spikes recorded in the left (d) and right (e) dentate gyrus during 30 min of immobility and slow wave sleep in rat 2, which showed uptake of AMT-MNPs in the right hippocampus; (f) peri-event time histogram for interictal spikes recorded in the left dentate gyrus versus right dentate gyrus. Most interictal spikes occurred on the right, the side of AMT-MNP uptake.

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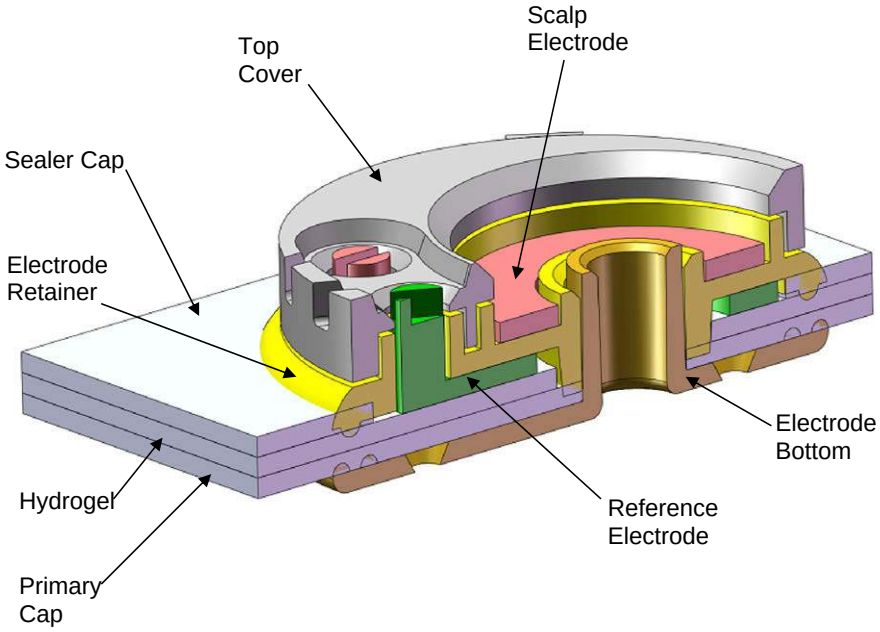

Fig. 3. Cutaway view of fEEG electrode and reference layer. The scalp electrode (pink) and reference electrode (green) are closely matched spatially to match loop areas, with a carbon wire pair (not shown) terminating at the connector posts on the left. The reference electrode is in direct contact with the reference layer (labeled "hydrogel") and is electrically insulated and sealed from the scalp electrode. Scalp prep is applied through the center hole in the assembly, with a small column of standard electrode gel used to make electrical connection from scalp to electrode. The "sealer cap" and "primary cap" are flexible and waterproof to allow a snug fit to the contours of the scalp and insulate the reference from the body.

blem is that the removal of gradient artifact is totally dependent on a precise prediction of the timing of the induced noise and its characteristics. This has required collecting the EEG and all induced noise using large-dynamic-range amplifiers, high sampling rates, and precision synchronization of the MR scanner and EEG clocks. The raw data thus collected have a very low signal-to-noise ratio (SNR) and must be postprocessed to recover usable EEG. Consequently the investment of time and technical expertise has been significantly greater than the quantity of acceptable EEG data recovered.

To eliminate synchronizing of MR and EEG clocks and reduce software processing of data, the SNR of EEG acquired during MR scanning must be raised significantly. As large scanner artifact enters EEG by means of time-varying magnetic fields inducing voltages on the loops formed by electrodes and lead wires, innovative analog noise cancellation techniques may be used to improve SNR prior to digitization. A natural progression from the classic EEG ear reference is to provide a matched reference for each scalp electrode, with a twisted wire pair connecting electrode and reference to a differential amplifier. If the reference signal is a matched version of the noise component appearing in the scalp channel, substantial reduction of noise may be effected by analog subtraction alone. The electrodes for the reference should not come into contact with the scalp; they should contact a reference layer that closely fits the contours of the head but remain electrically insulated from the body.

We have devised a flexible electrode cap with such a reference layer, one that closely approximates the electrical characteristics of the human scalp. The fMRI scanner artifact induced on each of the paired scalp and reference loops and electrodes (Fig. 3) is thereby closely matched. Raising SNR is accomplished by adaptive subtraction of the reference from the scalp signal in the EEG amplifier. Using this approach, we have been able to improve SNR by a factor of 10,000:1, and we are able to capture clean EEG without the use of postprocessing or clock synchronization. The residual BCG and scanner-induced artifact appearing in the amplifier output are removed as data are collected, using bespoke software algorithms operating in real time. EEG data are thereby displayed during scanning.

We have further developed a fully integrated 21-channel (currently) EEG system for use during fMRI scanning, known as fEEG [3]. Pending successful alpha and beta testing we envisage fEEG to enter the basic science and clinical research arenas in 2009, with subsequent entry into the clinical diagnostic arena following Food and Drug Administration approval, expected later in 2009.

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1.5. High-resolution brain SPECT: Meeting the challenge for confident lesion localization in refractory epilepsy

Eric M. Bailey

The reemergence of functional imaging tools such as PET and SPECT is due to advances in device quality and a proliferation of radioligand choices for neurological investigation. FDG, a metabolic PET radioligand, has shown promise in identifying hypo- and hypermetabolic regions associated with an epileptogenic focus [1]. SPECT has advanced with improved algorithms for performing subtraction interictal SPECT with the ^{99m}Tc blood flow radioligand [2]. This method works by enhancing the corresponding focal hypo (interictal)- and hyper (ictal)-perfusion.

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Although ictal SPECT has excellent temporal resolution (seconds), it has poor spatial resolution (7–10 mm) coupled with low-contrast sensitivity due to low photon counts. Much of this resolution limitation derives from the fundamental mechanical and mathematical approaches to detecting and tracing single photon emissions while dealing with interference from scatter photons. Although some improvement in spatial resolution has been made by the addition of "pinhole collimators," which can improve the accuracy of ray tracing, pinhole collimation limits photon detection angles, thus resulting in poor contrast sensitivity and the rejection of numerous formerly "good photons." Therefore, contrast sensitivity now becomes the limiting resolution element for SPECT.

SPECT perfusion imaging has been clinically successful for two decades in cardiovascular applications because these resolution drawbacks are insignificant compared with the macroscopic anatomy under evaluation. However, cerebrovascular applications, such as epilepsy, absolutely require solutions to these drawbacks because of the microscopic anatomy involved. We therefore determined that there would be significant clinical benefit in devising a high-resolution SPECT system optimized for brain imaging.

A new spin on an old design. The roots of nuclear medicine, now more popularly known as functional imaging, precede CT and MRI. However, the utility and performance of early PET and SPECT systems were dramatically limited by computer computational power. Tomographic reconstruction requirements in PET and SPECT are greater than an order of magnitude higher than those in CT and MRI. It was not until 2000 that computational power at an economical cost and speed was available to begin to satisfy the performance demanded of everyday clinical use.

With the above background, we looked back into the early age of SPECT and found a technique/device that was designed in the 1970s, originally by Union Carbide, as a brain-only high-resolution

Fig. 4. Picture of original high-resolution SPECT apparatus.

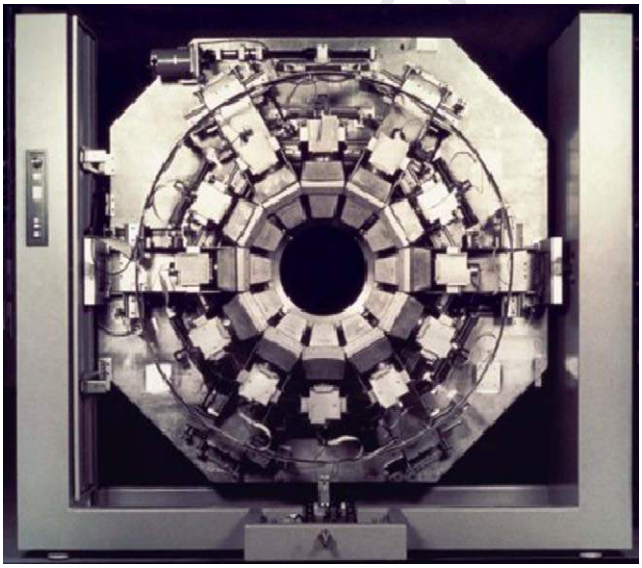

Fig. 5. Inside of original machine.

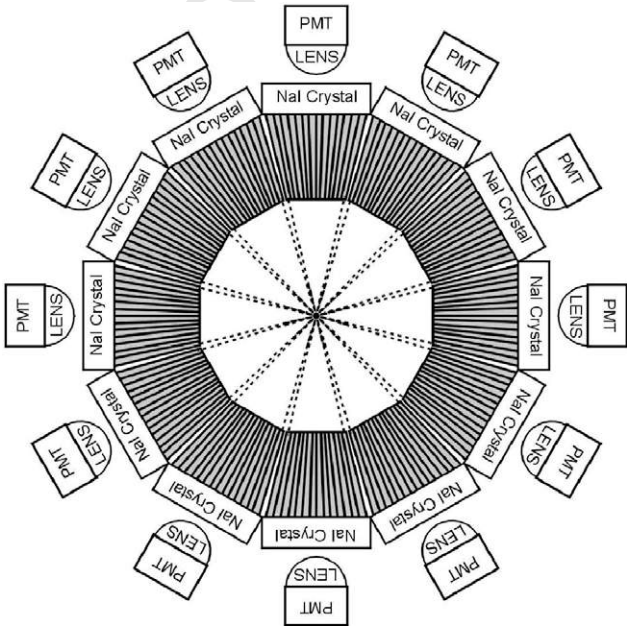

Fig. 6. Diagram of detectors and collimators.

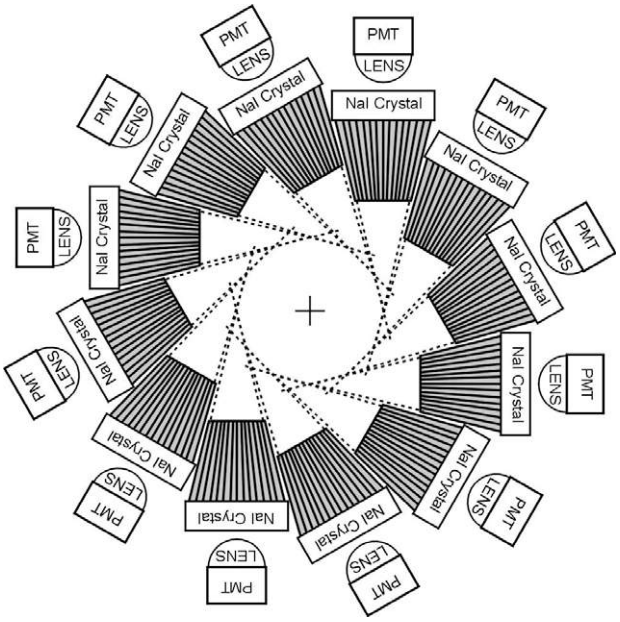

Fig. 7. Raster motion of "focal spot."

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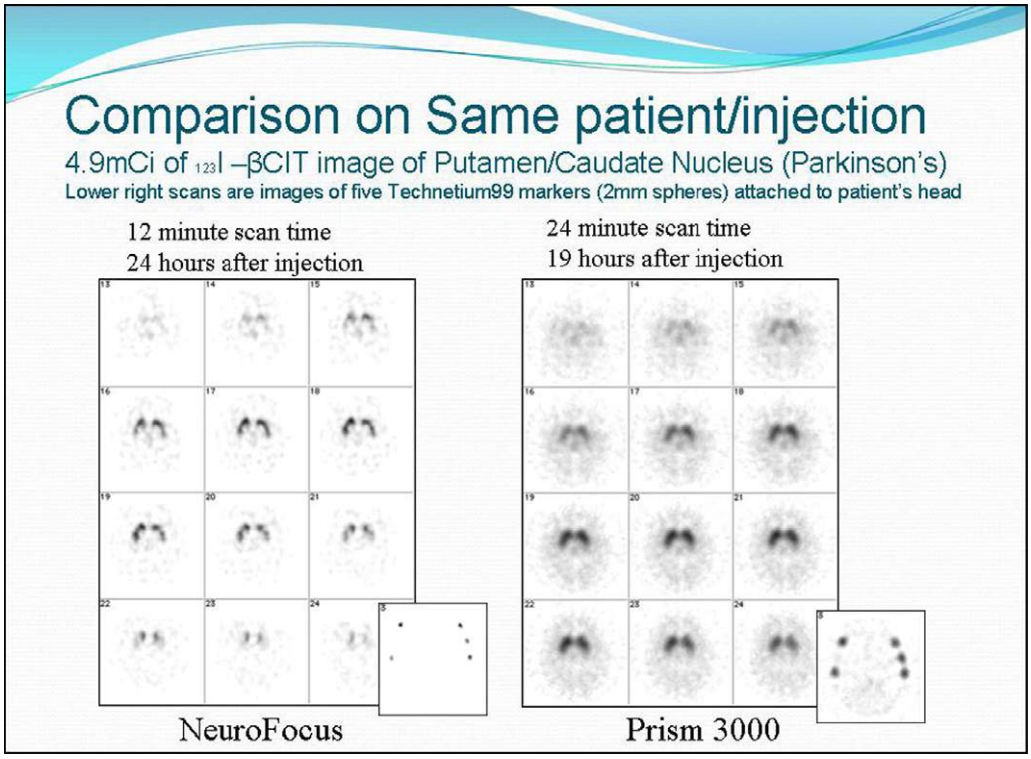

Fig. 8. Dopamine radioligand showing NeuroFocus on left versus standard SPECT system on the right. The small images are of small 1-cc radiomarkers placed on scalp for registration. Note the resolution difference in how standard SPECT tends to "blur" the signal.

SPECT system. Union Carbide, and then later Stryker Imaging, manufactured about 20 such machines before abandoning the technology. The machine works in a strikingly different fashion than traditional SPECT. The system is made up of 12 very large scintillator/photomultiplier tubes with a tapered "hourglass" collimator that basically focuses on a very small volume (1 cc) in the patient. By sweeping each detector's focal spot through the specimen from different angles, one gathers enough three-dimensional volumetric data for a tomographic solution. The analogy is that this device works more like a scanning electron microscope whereby a focal spot is rastered through the specimen to eventually produce a two- or three-dimensional image. The original machine was very large and heavy despite its small bore size and required a large room for permanent fixation (Figs. 4–7).

The original inventor, a Massachusetts native named Dr. Hugh Stoddart, reenergized the technology in the late 1990s by creating a three-dimensional tomographic reconstruction and applying it to some of the few machines still in existence. The result of the new algorithm was the highest-available-resolution SPECT image of the brain that showed greater than an order of magnitude more im-

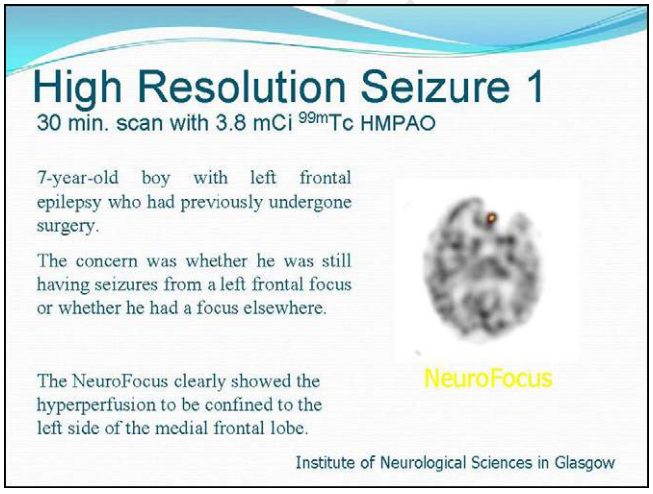

Fig. 9. Image of focal region of hyperperfusion in neurosurgical patient.

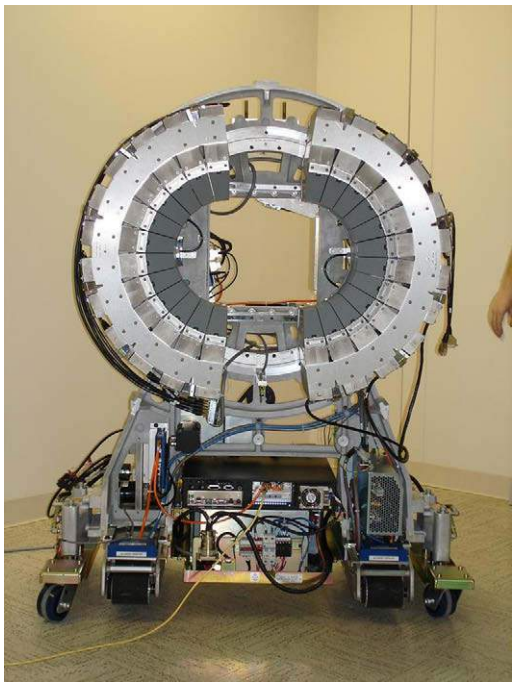

Fig. 10. Small, portable, high-resolution SPECT device (NeuroLogica Corp., Danvers, MA, USA) that can be brought into an epilepsy monitoring unit to scan a patient in the hospital bed.

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provement over conventional SPECT. Figs. 8 and 9 are images acquired with the new algorithm.

NeuroLogica Corporation in Danvers, MA, USA, acquired the rights to the algorithm intellectual property in 2004 and has redesigned the machine to be much smaller and portable. This was partly achieved by spinning the detectors in a similar fashion to X-ray CT. In addition, the detectors were segmented into 72 (versus the original 12) with the possibility of achieving even greater resolution/sensitivity. The result is a small, portable, high-resolution SPECT device that can be brought into an epilepsy monitoring unit to scan a patient in the hospital bed, thus avoiding the complications/costs of patient transport (see Fig. 10).

Besides ^{99m}Tc perfusion imaging, the system will be capable of scanning with virtually any other present or future SPECT radioligand. The exciting possibility is that one day we may be able to produce scans of other neurotransmitters, plaques, proteins, etc., that play a role in epilepsy and neurodegenerative diseases.

In conclusion, NeuroLogica submitted its FDA 510k in March 2009 and hopes to have FDA commercial clearance by July 2009.

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1.6. Patient-specific EEG models, diffusion tensor imaging, and tractography: A pipeline for pediatric epilepsy surgery planning

Olivier Commowick, Simon K. Warfield

Approximately 75% of patients with epilepsy have their first seizure in childhood. Many do not become candidates for surgical intervention until after long trials of partially effective medications, which can have debilitating educational and sociological side effects. There is therefore increasing interest in early and effective surgical intervention to prevent these and other consequences of intractable epilepsy.

Accurate identification and localization of lesions are critical to improved surgical intervention [1]. Advances in computer capacity and imaging technology have created an environment in which a significant impact on patient care can be reached by developing a noninvasive localization strategy. We are developing imaging and individualized analysis algorithms to improve the detection and localization of epileptogenic foci, which will enable curative surgery for more patients. Moreover, we are developing techniques to detect the presence of important structures surrounding the lesion. These advances are designed to significantly improve surgical outcomes, that is, the number of patients with no or dramatically fewer seizures following surgery, without the risks of the invasive procedures typically performed in the presurgical evaluation.

Our pipeline is based on high-resolution images. High-resolution T1, T2, and FLAIR images ($1 \times 1 \times 1$ mm^3) are acquired on a Siemens 3T scanner, as are functional MR and diffusion tensor images ($2 \times 2 \times 2$ mm^3, 35 directions). In addition, EEG is acquired using a specific acquisition net of 128 channels instead of the commonly used 32-channel net. This large number of electrodes yields a much more accurate source localization.

The images are then fused to combine their specific information. First, the anatomical images (T2, FLAIR) are registered on the T1 image using a rigid transformation [2]. To correct for diffusion tensor imaging (DTI) distortion, the DTI mean diffusivity is registered rigidly on the T1. Then, an additional step of nonlinear registration [3] is added to recover local deformations and applied to the DTI [4].

The aligned images are then used in advanced patient-specific models for EEG source localization such as proposed in Refs. [5–10]. These models use patient-specific prior information on tissue class diffusivities, obtained from the T1, T2, and FLAIR images [11]. Moreover, these models can be combined with electrical conductivity fields derived from diffusion tensor MRI [12]. DTI is therefore used to determine accurate conductivity inside the white matter. Interestingly, DTI may also be used to detect abnormal tracts connecting several seizure foci, providing anatomic correlations for EEG spikes. These processes produce very accurate EEG source localization.

The second part of the pipeline is the detection, using DTI and fMRI, of crucial regions, such as the motor regions or some specific fiber tracts. Activation regions (related to motor tasks or other important tasks) are then computed from functional MRI (using SPM; http://www.fil.ion.ucl.ac.uk/spm/) and important tracts are extracted from DTI with a stochastic tractography algorithm [13].

With these tools, patient-specific surgical planning can be achieved. Fig. 11 shows how the information from modalities such as T1, DTI, and fMRI can be fused: Fig. 11a illustrates the fusion of motor cortex activation and the T1 image, and Fig. 11b, the fusion of DTI fractional anisotropy [14] with T1. Both of these representations are important as they give information on the location of fibers or important cortical regions. Fig. 11c illustrates an even

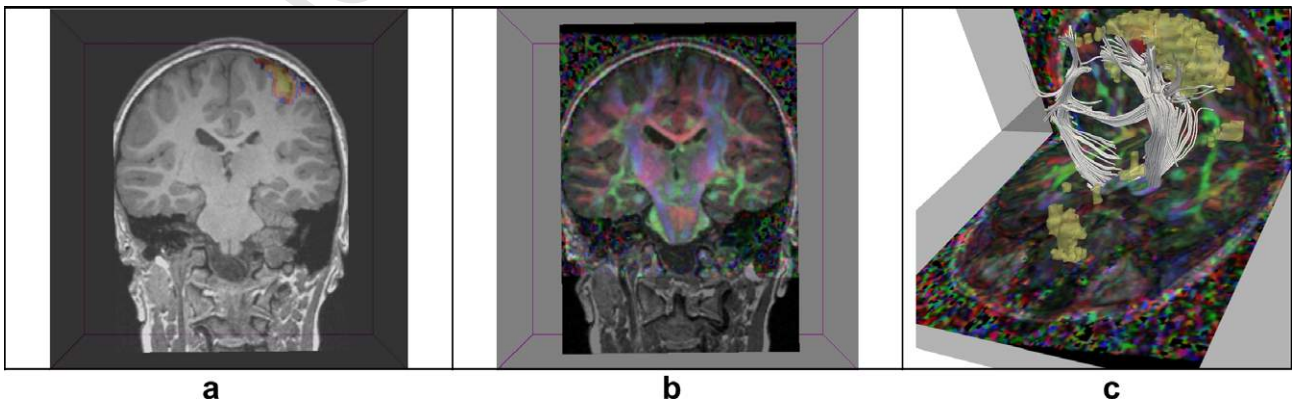

Fig. 11. Illustration of fused images for surgery planning. T1 and functional MRI activation region (a); T1 and colored fractional anisotropy (b); DTI, tractography and T1 image (c).

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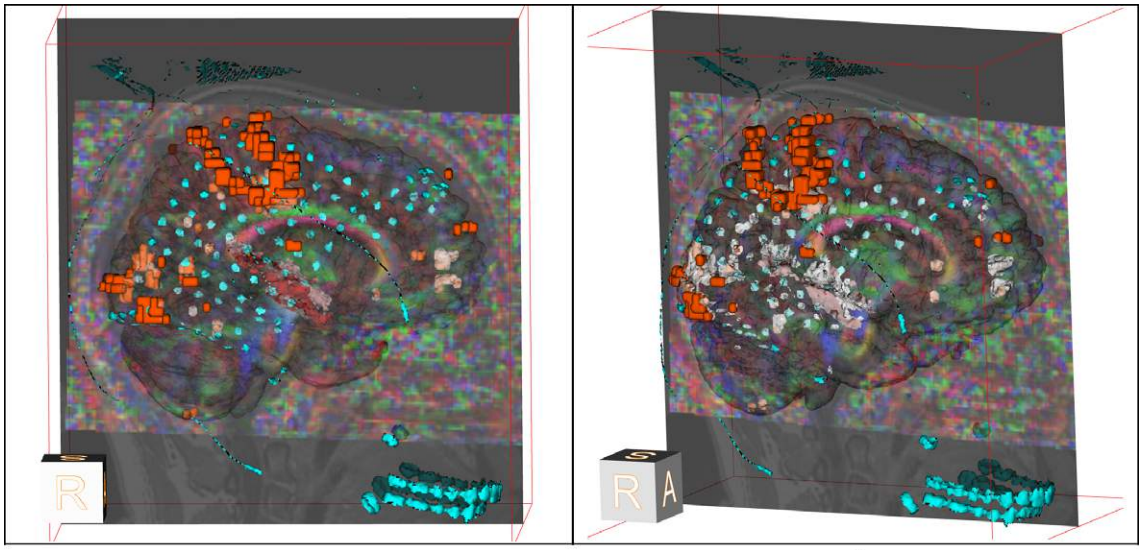

Fig. 12. Illustration of intracranial EEG-based surgical planning. Blue, electrodes; orange, right-hand activations; gray, left-hand activations; red, lesion.

more complete example of fusion, showing activation regions (in yellow and red) as well as major fiber tracts.

Finally, this pipeline is also used for surgery cases that required intracranial EEG recording. In this situation, the electrodes can be segmented from a CT scanner image and registered to the T1 image of the patient using rigid registration. Fig. 12 is an example of surgical planning, showing the electrodes used for the EEG acquisition in blue, activation regions for the left and right hand, respectively, in gray and orange, and the lesion in red. This type of surgical planning visualization is crucial, allowing the surgeon not only to see in three dimensions which electrodes were activated in the EEG, but also providing very complete information on the important regions of the brain and the lesion position.

In conclusion, we have developed a set of software tools for data fusion, segmentation, registration, and visualization. These tools are used in a pipeline to provide accurate planning for pediatric epilepsy surgery by identifying both the crucial regions (important functional cortex, white matter tracts) and the lesions to be removed by the resolution of the EEG inverse problem with patient-specific models. This approach allows the surgeon to choose the safest way to remove the lesion. Ultimately the accurate localization of the lesions and crucial areas may enable the use of minimally invasive interventions, such as electrical disruption with fine wire electrodes, focused ultrasound, and microwave ablation, which could represent a dramatic improvement as compared with open surgery.

We plan to develop automatic lesion segmentation algorithms from measures such as cortical thickness, unusual cortical folding, and DTI-based measures (e.g., detection of tensor abnormalities with respect to controls and detection of unusual fiber tracts). This last step will lead to a fully automatic pipeline to give the surgeon an evaluation of the patient's specific anatomy.

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1.7. Near-infrared spectroscopy and epilepsy

Anne Gallagher, Renée Béland, Franco Lepore, Dang Khoa Nguyen, Maryse Lassonde

Near-infrared spectroscopy (NIRS) is a relatively new technique that measures hemodynamic changes associated with neural activity during brain activation [1]. Cerebral activation induces blood flow fluctuations, leading to changes in oxyhemoglobin (HbO) and deoxyhemoglobin (HbR) concentrations. HbO and HbR present different absorption coefficients for near-infrared light. Simultaneous use of two different wavelengths between 680 and 1000

nm (near-infrared spectrum), each being more specific to the HbO (e.g., 830 nm) and HbR (e.g., 690 nm) absorption coefficients, allows independent measurement of concentration changes of HbO and HbR in living tissues [2]. Basically, near-infrared lights are directed through optic fibers attached to the patient's head. Based on the amount of detected light and using a modified Beer–Lambert law, it is possible to estimate the amount of absorption of the two wavelengths, which reflect changes in HbO and HbR concentrations in targeted cerebral areas (for a more detailed description of the method, see [3,4]).

NIRS may potentially contribute to the presurgical evaluation of language lateralization and localization of the epileptogenic zone in patients with epilepsy. Indeed, NIRS has been successfully used to assess language laterality in healthy adults [5,6] and adults with epilepsy [7,8], as well as children [9–11]. In all these studies, NIRS results were congruent with fMRI or Wada test results. Kennan et al. [5] showed that NIRS can be used in healthy adults to assess lateralization of activity in the prefrontal area during a semantic and syntactic decision task. The authors reported a strong correlation between the laterality indices calculated using NIRS and fMRI in all six participants. In another study, Watanabe et al. [7] showed perfect concordance between NIRS and Wada test language lateralization indices across six adults with epilepsy who performed a verbal fluency task during NIRS recording.

In our laboratory, we recently compared NIRS results obtained while participants performed a verbal fluency task with those obtained by fMRI and/or Wada test in two healthy adults, two adults with epilepsy, and four children with epilepsy [9]. We obtained a perfect concordance of language dominance between both NIRS and fMRI, and NIRS and the Wada test. We also obtained clear NIRS results in two children for whom the Wada test and fMRI could not be performed because of the very young age (3 years) of one child and another with pervasive developmental disorder with moderate mental deficiency. Although neither child could remain motionless during NIRS data acquisition, data analysis was not compromised, indicating that NIRS has a high tolerance to body movements.

Because of the importance of assessing hemispheric language dominance for both expressive and receptive language, we also used NIRS to assess both types of language in a 9-year-old boy with a probable left temporal seizure focus undergoing a presurgical evaluation who could tolerate neither the Wada test nor fMRI because of language problems and anxiety [10]. A verbal fluency task revealed left hemisphere dominance, including both Broca and Wernicke areas, reflecting an intrahemispheric cerebral reorganization for expressive language. During the receptive language task, which involved passive listening to a story, a bilateral temporofrontal activation was recorded, suggesting intra- and interhemispheric cerebral reorganization for receptive language. These studies indicate that NIRS can be useful in presurgical language investigation with pediatric or mentally challenged patients.

With respect to using NIRS to localize the epileptogenic zone for epilepsy surgery candidates, Watanabe and colleagues [12,13] applied NIRS monitoring to successfully measure changes in cerebral blood flow during spontaneous seizures in 2 patients and bemegride-induced seizures in 26 (mainly adult) patients with refractory partial epilepsy. They placed 8–24 NIRS channels over the prospective focus region. More recently, our group recorded spontaneous seizures from a 10-year-old patient with refractory MRI-negative right frontal epilepsy using 128 NIRS channels [11]. A clear activation was obtained using simultaneous EEG–NIRS in the right frontal region during seizures. In this patient, EEG–NIRS results were in very good concordance with the data obtained from other functional imaging techniques (SPECT, FDG-PET, EEG–fMRI, and EEG–MEG).

NIRS presents many advantages over other imaging methods [3,14–16]. It is noninvasive, more resistant to movement artifacts, and can easily be performed in young patients, including infants [17,18]. In contrast with fMRI and MEG, which both require covert articulation, the expressive language tasks used with NIRS can involve overt articulation without the physical constraints that impede articulatory gestures. During data acquisition, the child is seated in a chair or on the parent's lap to allow direct contact with the experimenter. Also, the equipment is portable, allowing bedside assessments [19,20], and is much less expensive than fMRI or PET, with better temporal resolution than SPECT and fMRI. Finally, it provides quantitative information about total Hb, HbO, and HbR compared with fMRI BOLD signal based principally on HbR variations.

The main disadvantage of NIRS is the shallow penetration of the photons (between 3 and 5 cm). This impedes reliable data recording of subcortical activations (e.g., thalamus). The development of algorithms that increase the signal-to-noise ratio to allow deeper cerebral structures to be studied is now in progress. However, spatial resolution in most patients is currently no better than 1 cm, which is much less precise than fMRI.

Many additional tools remain to be developed in hardware, software, and data analysis, especially to generate tomographic representations. Future studies should cover the whole scalp more extensively, especially to localize the epileptogenic zone. For some patients, careful revision of MRI guided by NIRS could detect subtle epileptogenic lesions previously missed by visual inspection of MR images. For others, EEG–NIRS combined with classic and other novel noninvasive techniques may reduce the need for invasive monitoring. For those patients who still require an intracranial study, NIRS can potentially allow more accurate electrode positioning or reduce the extent of the studied zone. Moreover, NIRS has the potential to become a viable, noninvasive alternative to the Wada test in the determination of speech lateralization in children and other patients unable to remain motionless or who are reluctant to submit to more invasive techniques.

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1.8. A device for real-time functional mapping using electrocorticography

Gerwin Schalk, Peter Brunner, Anthony L. Ritaccio

Localization of cortical function is frequently performed in patients with medically refractory epilepsy to identify eloquent cortex prior to excision of the epileptogenic zone. Existing techniques of functional mapping include those that assess regional metabolic changes (fMRI and PET), record fluctuations in neuronal magnetic fields (MEG), and deliver electrical cortical stimulation (ECS), which is the "gold standard" that has been in use since 1874 . These complementary systems are hindered by different factors such as cost, practicality, morbidity, and time. ECS is a common, but nonstandardized, tool whose application is complicated by risk of afterdischarges and seizures, long-time commitment, maturational factors in children, and oversimplified assessments due to temporal restrictions (typical 10-s stimulation train) [2].

Over the past decade, offline analyses of passive recordings of electrocorticographic activity (ECoG) have demonstrated task-related gamma (40–200 Hz) activity changes, whose topographic and temporal patterns are consistent with the functional anatomy and processing dynamics of sensorimotor, auditory, visual, and language function . Further, gamma band modulations evident in ECoG correlate tightly with hemodynamic signals, specifically BOLD variations on fMRI . The practical attractiveness of functional mapping by recording macroscopic local field potentials representing neuronal populations involved in a specific task has been similarly limited by the usual need for highly trained personnel and sophisticated offline analysis techniques.

To address this problem, we recently described a novel signal processing and visualization method called SIGFRIED (signal modeling for real-time identification and event detection) that uses passively recorded ECoG activity to detect task-related activity in real time. The critical advantages of the SIGFRIED method are that it does not require prior data collection from all relevant tasks or any subject-specific parameter settings. To operate this method at the bedside, we implemented the SIGFRIED method within the BCI2000 system , which is a general-purpose software system for real-time biosignal acquisition, processing, and feedback. BCI2000 currently supports more than 10 different data acquisition devices and operates on any current Windows-based laptop or desktop computer. Because it is very robust and integrates well in clinical environments, the BCI2000/SIGFRIED system for functional mapping has already been adopted by several epilepsy clinics in the United States and Europe. It initially requires the collection of a short (about 3 min) baseline. Afterward, subjects are asked to engage in different motor or language tasks, such as moving the hand or the tongue, in response to visual cues. A computer screen visually displays an electrode topography for each of the tasks. The topographies contain circles at the electrode locations (see Fig. 13). The radius of each circle is proportional to the ECoG signal change (usually in high gamma frequency bands) for the respective task compared with the base-

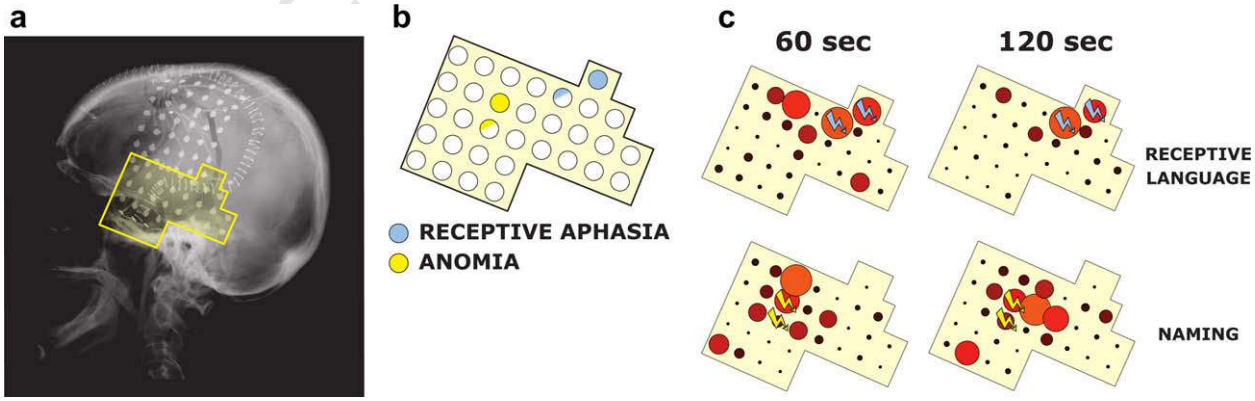

Fig. 13. (a) Lateral radiograph and sketch of locations of recorded subdural electrodes. (b) Results of electrical stimulation mapping that were gathered over 5 h. Blue and yellow circles indicate sites that produced receptive aphasia and anomia, respectively. (c) Results of ECoG-based real-time mapping that were gathered in only 2 min. The subject performed a receptive language and naming task in response to visual cues. The SIGFRIED package visualized the change in ECoG signals in mu/beta frequencies (compared with a previously recorded baseline) in real time. Two columns of figures show the display to the investigator at 60 and 120 s. The results of the passive real-time mapping of language are concordant with the results of electrical stimulation (see blue and yellow arrows corresponding to receptive language and naming, respectively).

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line period recorded earlier. Thus, by use of the SIGFRIED/BCI2000 system, clinically relevant mapping of linguistic and sensorimotor function is achievable at the bedside in minutes. In a recent multicenter study [10], we found that the SIGFRIED procedure identifies at least the same contacts or their immediate neighbors compared with ECS mapping.

The past decade has seen a greatly expanded understanding of task-related ECoG changes. Although the exact relationship between passive ECoG-based mapping and conventional ECS-based mapping is not yet clear, it is likely that passive mapping will play an important role in the near future. Thus, we believe that based on its procedural simplicity, rapidity (minutes), safety (passive recording), and relatively low expense, our methodology has the potential to complement and potentially replace currently used clinical methods.

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2. Seizure onset detection and seizure prediction

2.1. Overview

John Guttag

Seizure onset detection involves detecting some physiological indication that a seizure has already commenced. Seizure prediction involves an assertion that, with high probability, a seizure will occur within a specified window of time. When seizures occur at inopportune moments, patients can suffer severe accidents. If seizures could be predicted with high accuracy or detected prior to the onset of debilitating clinical symptoms, patients could be warned to remove themselves from potentially dangerous situations. Additionally, caregivers could be summoned to provide assistance. The advent of pharmacological (e.g., sublingual lorazepam) and nonpharmacological (e.g., neurostimulation) therapies exhibiting rapid antiseizure effects increases the likelihood that the acute effects of seizures can be mitigated outside clinical environments. Though the efficacy of these interventions has yet to be fully quantified, evidence suggests that efficacy improves with early intervention. Automated detection systems could be used to prompt patients to take action or be used as part of closed-loop drug delivery or neurostimulation devices. In addition, a sufficiently good onset detector could both reduce cost and improve results in the acquisition of ictal PET or SPECT scans by ensuring the timely injection of a radiotracer.

Assume that time is divided into consecutive epochs of fixed duration. A gold standard is the labeling of each epoch as part or not part of a seizure. Such a standard is not easy to come by. Experts sometimes disagree about what constitutes a seizure, and they frequently disagree about which epoch is the first that should be thought of as part of the seizure. For example, is it the first epoch with an observable clinical symptom, or the first epoch for which an EEG shows an epileptiform discharge? In evaluating prediction and detection methods, one must first decide which time epochs to consider. For example, many seizure onset detectors perform poorly during postictal periods, and many studies choose to ignore such periods.

An onset detector labels each epoch as belonging or not belonging to the onset of a seizure. A key question in evaluating such a detector is whether to focus on correctly identifying epochs or correctly identifying events. For example, once an onset detector has declared that a seizure has started, does it matter whether it labels subsequent windows as seizure onset? For concreteness, we focus on events here, but the translation to epochs is a simple one.

The "goodness" of a seizure prediction or detection method cannot be discussed independently of the applications in which it might be employed. However, the notions of sensitivity, specificity, and latency are often relevant in evaluating such methods. Loosely speaking, sensitivity can be thought of as the fraction of true events that are detected. This can be defined simply as the number of seizures for which the method has labeled at least one epoch as seizure, divided by the total number of seizures. Similarly, specificity can be defined as the number of nonconsecutive epochs that are mistakenly classified as belonging to a seizure, divided by the total number of epochs of nonseizure data. This can be translated into the number of false alarm events per seizure-free hour.

Latency is the number of epochs between the time a seizure begins, for example, as determined by EEG, and the time it is detected. By definition, latency must be nonnegative. Of course, it is possible to detect electrographic onset prior to clinical onset or intracranial EEG onset prior to scalp EEG onset.

One can usually increase specificity at the cost of decreased sensitivity and/or increased latency. In balancing these trade-offs, one needs to consider the application. If overtreatment is not a concern (e.g., for a closed-loop neural stimulator), it might make sense to maximize sensitivity and minimize latency. However, when used to control injection of a radiotracer, the detector should probably be optimized to maximize specificity.

Sensitivity and specificity are more complicated to define for seizure prediction. A careful discussion can be found in Ref. [1]. Here we try to give a flavor of the issues.

A seizure prediction algorithm can be modeled as assigning to each epoch a triple, $\langle P, E_1, E_2 \rangle$, where P is the probability that a seizure will start somewhere between E_1 and E_2 epochs from the time of prediction. We call this interval the prediction window. For simplicity of description, we assume here that P is either 0 or 1. (Note that when $E_1 = E_2 = 0$, prediction and detection are the same problem.)

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Roughly speaking, sensitivity can be thought of as the fraction of events that begin within a prediction window. Specificity is more complicated. Defining specificity in terms of the number of false alarms is problematic; for example, choosing extremely large prediction windows allows for near-perfect sensitivity and specificity, without providing clinical utility. It seems better to think of specificity as capturing the fraction of a patient's time spent anticipating an imminent seizure. A rough measure of this is the sum of the number of epochs in predication windows divided by the total number of epochs.

The prediction and timely detection of epileptic seizures are related, but different, problems with important clinical applications. As the articles in the rest of this section indicate, there are active and productive research programs aimed at both problems. The reader may be a bit frustrated by the incomparability of some of the reported results, but this is typical of the literature. It would be helpful if the community developed standard data sets and standard metrics that facilitated more direct comparison of different approaches.

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2.2. The journey from seizure prediction to seizure control with an intermediate stop for focus localization

Leon D. Iasemidis

Until recently, the general belief in the medical community was that epileptic seizures could not be anticipated. Seizures were assumed to be abrupt transitions that occurred randomly over time. However, theories based on clinical reports and scientific intuition, like the "reservoir theory" postulated by Lennox [1], existed and pointed in the direction of seizure predictability. Various feelings of auras, that is, patients' reports of sensations of an upcoming seizure, also exist in the medical literature. Penfield [2] was the first to note changes in cerebral blood flow prior to seizures. Deterministically predictable occurrences of seizures (reflex seizures) in a small minority (about 3–5%) of patients have been reported as a result of various sensory stimuli [3]. These theories and facts implied that seizures might be predictable. The ability to predict epileptic seizures well ahead of their occurrence may lead to novel diagnostic tools and treatment for epilepsy (see [4] for a review).

The 1980s saw the emergence of new signal processing methodologies [5–7], based on the mathematical theory of nonlinear dynamics for the study of spontaneous formation of organized spatial, temporal, or spatiotemporal patterns in physical, chemical, and biological systems. These methodologies quantify the complexity and randomness of the signal from the perspective of dynamical invariants like dimensionality and entropy rate, respectively, and represent a drastic departure from the signal processing techniques based on the linear model (e.g., Fourier analysis).

The existence of long-term preictal periods (order of minutes) was initially shown using nonlinear dynamical analysis of EEG from subdural arrays in patients with epilepsy [8] over the temporal and frontal lobes, and later from scalp and intracranial (e.g., hippocampal) electrodes [9,10]. Monitoring the temporal evolution of the short-term Lyapunov exponents (STL_{max}, measures of chaos and instability of a system) at critical brain sites showed that a progressive preictal increase of convergence of STL_{max} was a precursor to epileptic seizures [11–16]. Subsequently, phases at critical brain sites showed similar behavior [17,18]. We called this convergence of measures of dynamics *dynamical entrainment* or *dynamical synchronization*. These observations have been successfully implemented in the prospective prediction of epileptic seizures with reported average prediction times of 70 min before a seizure, sensitivity (percentage of predicted seizures) above 85%, and a false prediction rate of approximately 0.1 false warning per hour [19–25].

This initial success in seizure prediction also has produced significant by-products for epilepsy research that relate to epileptogenic focus localization (diagnosis), ictogenesis (the development of seizures), and control of seizures (treatment). In particular, it was found that the majority of seizures (81%) in patients with temporal lobe epilepsy (TLE) irreversibly reset (disentrain) the observed preictal dynamical entrainment postictally [26–30]. This finding, combined with that from the observed no resetting or reduced resetting of brain dynamics during the preictal period, implies that seizures occur when there is a need to reset the pathology (long-term entrainment) of brain dynamics. We have called this hypothesis the "seizure resetting hypothesis" and it could help answer the question of why seizures occur.

The manner in which this resetting is accomplished by the epileptic brain remains to be investigated. It may reflect a passive mechanism: high electrical activity during a seizure might deplete critical neurotransmitters and/or deactivate critical neuroreceptors in the entrained neuronal network. An alternative explanation is that release of neuropeptides (e.g., inhibitory neurotransmitters) in the brain, due to seizure activity, may contribute to the temporary repair of the pathological internal feedback networks. Seizures themselves may also fail to reset the brain, as may be the case with status epilepticus (SE), where subsequent seizures fail to reset the brain. Recent results on SE in this context from humans and rodent models of epilepsy support this conjecture. They also show that successful recovery from SE through administration of antiepileptic drugs (AEDs) is possible only if the AEDs reset the brain dynamics [28].

A by-product of the seizure prediction technology relates to focus localization. It was found that brain sites in the epileptogenic focus (focal zone) are the ones that most frequently participate in the observed preictal entrainment, suggesting that the focus could be identified from the preictal period well before seizure onset [31]. Furthermore, by use of a similar dynamical analysis with appropriate modifications, it was recently shown from intracranial and scalp EEGs of patients with focal epilepsy that interictal entrainment of dynamics also takes place, and is more frequent in the area of the epileptogenic zone [32]. This, of course, raises the possibility of a reliable localization and lateralization of the epileptogenic focus from short interictal periods on an outpatient basis without the need for long-term (days) EEG monitoring and recording of multiple seizures.

Employing neuronal population models that are capable of exhibiting seizure-like behavior, we have shown that entrainment between the populations' STL_{max} with increased coupling resembles the observed preictal dynamical entrainment of STL_{max} at critical sites in the epileptic brain [33–36]. In agreement with burst phenomena in adaptive systems, "seizures" in these models occur if the existing (internal to the models) feedback loops are pathological so that they lack the ability to compensate fast enough for excessive increases in the network coupling. This situation eventually leads to seizurelike transitions. Motivated by these findings, we postulated the existence of an internal pathological feedback action in the epileptic brain. Subsequently, using a control-oriented approach, we developed a functional model for an external seizure controller. During periods of abnormally high synchronization (entrainment), the developed control scheme provides appropriate "desynchronizing feedback" to maintain "normal" synchronization levels between neural populations (homeostasis of dynamics).

Please cite this article in press as: Schachter SC et al. Advances in the Application of Technology to Epilepsy: The CIMIT/NIO Epilepsy Innovation Summit Epilepsy Behav (2009), doi:10.1016/j.yebeh.2009.06.028

Such results directly address the quest for seizure control. They appear to support the hypotheses that: (1) seizures may result from the inability of internal feedback mechanisms to provide timely compensation/regulation of coupling between brain sites, and (2) seizure control can be achieved by feedback decoupling of the "pathological" sites via externally provided appropriate stimuli. Such stimuli are functions of both the EEG and the coupling of the respective brain sites. We have called such a closed-loop control scheme *feedback decoupling*.

According to this theory of epileptogenesis, the basic macroscopic dynamics for a "normal" brain are: (1) brain in spatiotemporal chaos; (2) stimulus enters the system and changes the spatial coupling between two or more brain sites; (3) spatial coupling produces spatial correlations, possibly storing the information about the stimulus and/or initiating action; (4) spatial correlations also activate an internal compensating feedback mechanism; (5) the compensation removes (or assimilates) the developed spatial correlations by the stimulus within a short time interval; and (6) the system returns to spatiotemporal chaos. In the "normal brain," the correlations in the network must lie within a "normal" range and be able to vary quickly in response to a stimulus, which implies that the internal feedback path should be well tuned and be able to track changes of the coupling reasonably closely. Accordingly, we have proposed that the "epileptic" brain has pathological (poorly tuned) internal feedback paths. Such pathology exhibits large errors in the estimates of the coupling, and can cause local destabilization and bursting of the network (seizures). Thus, the observed long-term dynamical entrainment prior to seizures can be interpreted as an indicator of pathology and inability of the internal feedback network to compensate. The above rationale can, of course, easily explain the existence of "reflex" epilepsies as well.

In summary, from our group's past and ongoing research on the dynamics of epilepsy, the following three central concepts about epileptic seizures have emerged. *First*, we have shown that seizures are manifestations of preictal recruitment of brain sites in an abnormal hypersynchronization. The onset of such recruitment occurs long before the onset of a seizure—on the order of minutes for seizure prediction and on the order of hours to days for detection of seizure susceptibility. *Second*, resetting of the preictal dynamical recruitment is observed postictally, and more probably starts at the seizure's onset. Complete or partial resetting of the preictal entrainment of the epileptic brain at a seizure may affect the route to the subsequent seizure. No resetting or partial resetting may explain SE and the observed nonstationary nature of seizure occurrences. *Third*, through control-oriented modeling, a feedback control view of epileptic seizures has been postulated, wherein epileptic seizures are hypothesized to be a result of the inability of the internal feedback/regulatory mechanisms of the brain to track and disrupt excessive synchronization between the epileptogenic focus and other brain areas prior to a seizure.

All the above concepts are interrelated, and constitute the basis for development of seizure prediction algorithms, epileptogenic focus localization algorithms, and first-generation closed-loop control algorithms. These concepts may provide the key ingredients for the development of robust brain pacemakers for the treatment of epilepsy in the near future. Appropriate electromagnetic stimulation and/or administration of AEDs at the beginning of the preictal period may disrupt the observed dynamical entrainment of normal brain sites with the epileptogenic focus and lead to a significant reduction of the rate and severity of epileptic seizures [37]. In addition, these concepts can be used for evaluation of the efficacy of existing AEDs and the design of new ones. Finally, as it has now been shown in SE, the developed measures and methodology could be used as stand-alone or incorporated into medical devices as monitoring tools for the evaluation of seizure susceptibility, as well as for other significant diagnostic purposes, like localization of the epileptogenic zone and differential diagnosis of epilepsy.

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2.3. Seizure prediction and monitoring

J. Chris Sackellares

Why seizures come and go remains unanswered. In 1988, Sackellares and Iasemidis tested the hypothesis that the transition from the interictal state to a seizure (ictal state) is similar to the state transitions observed in chaotic systems [1–4]. They found that the spatiotemporal patterns of the ictal states were consistently more ordered than that of the interictal and postictal states. Further, there was a significant change in measures of spatial order of EEG signals that precede seizures by periods on the order of an hour. Thus, by combining measures of temporal order, spatial order, and signal energy, it became possible to develop devices that can predict as well as detect seizures.

Seizure prediction and seizure detection devices have a wide range of potential clinical applications that depend on their sensitivity and false prediction or detection rates. These applications include patient monitoring in venues such as epilepsy monitoring units, intensive care units, and emergency departments. They also may be incorporated into closed-loop seizure control devices. Preliminary studies in the rodent chronic limbic epilepsy model indicate that the development of seizures, once detected, can be reversed by electrical stimulation of the brain, thereby delaying or even preventing seizure occurrence.

These scientific discoveries led to the development and testing of patented methods for automated seizure detection and prediction algorithms, and novel methods for their use in implantable seizure control devices. The methods use spatiotemporal patterns derived from EEG dynamics, including linear and nonlinear, uni- and bivariate EEG descriptors. An important finding is that the transition before a seizure occurrence (i.e., so-called *preictal transition*) can be characterized by (1) progressive convergence of the mean short-term maximum Lyapunov exponents (STL_{max}) among specific anatomical areas (mean value entrainment), and (2) progressive phase locking of the STL_{max} profiles among various electrode sites (phase entrainment). In initial studies, preictal entrainment of EEG dynamics among electrode sites was detected by visual inspection of STL_{max}-versus-time plots. More recently, methods have been developed that provide objective criteria of pattern recognition for dynamical entrainment among electrode pairs [5]. On the basis of these findings, algorithms have been developed for the automatic detection of the preictal state for prediction of impending seizures [6–9].

Although the initial application of these methods was for intracranial EEG recordings, we have developed a scalp EEG-based automated seizure monitoring system that exhibits high seizure detection sensitivity with a low false detection rate. The detection algorithm uses measures of signal energy, frequency, and pattern regularity to capture characteristic ictal morphological features [10]. Nonlinear techniques are used to detect seizures, whereas linear features are used to reject recording artifacts and normal physiological activities (e.g., sleep transients and muscle and chewing artifacts). The algorithm also recognizes onset patterns (i.e., left unilateral, right unilateral, or bilateral) based on the spatial distribution of the EEG dynamics.

On the basis of this technology, Optima Neuroscience is producing a line of brain monitoring products designed for use in hospital emergency rooms and intensive care units. In U.S. emergency rooms, more than 10 million patients are evaluated annually with head trauma, transient ischemic attacks, and strokes. Because of the limited availability of EEG diagnostics, an alarming percentage of these patients develop unrecognized seizure activity causing further neuronal damage and loss of function. Optima's monitors will help automate the process of EEG interpretation, greatly improving the identification of subclinical seizures and reducing the current time delay to treatment initiation.

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Optima's seizure detection and prediction technology will also be used to improve the efficiency of reviewing long-term EEG recordings. This software marks the areas of interest (spike and seizures) with a higher sensitivity and lower false positive rate than commercially available products, which translates into dramatic time savings compared with manually screening multiple days of EEG recordings. When used online in an epilepsy monitoring unit, our software can help shorten hospital stays by notifying the staff as soon as the requisite number of events has been recorded.

Similar algorithms are being developed by our research team to detect a wide range of normal and abnormal brain wave patterns. These algorithms are applied to the detection of EEG patterns that occur during stroke, impending stroke, hypoxia, hypoglycemia, and other metabolic disorders that alter brain function. These algorithms will be incorporated in the same brain monitoring systems used to detect and predict seizures. The systems can be used in a variety of settings including special diagnostic and treatment units, intensive care units, emergency departments, postoperative recovery rooms, general care hospital beds, emergency vehicles, and even in the home.

Optima Neuroscience is nearing the completion of a clinical study evaluating the sensitivity and false positive rate of the automated seizure detection algorithms. We are using a large sample of long-term EEG recordings and comparing the performance of our algorithm with that of commercially available products. Once cleared by the FDA, this technology will be available to EEG specialists as a software package to improve the efficiency of EEG review. Development is underway to design a clinically useful brain function monitor using the same core analysis techniques. Designed for use in intensive care units, emergency rooms, and epilepsy monitoring units, the portable stand-alone monitor will increase the availability of EEG diagnostics. This system will record and monitor the brain's electrical activity and provide critical brain function information, including seizure warning and detection. In later generations, the system will include alerts and detections of other threatening brain conditions such as ischemia (reduced blood supply and impending stroke), hypoglycemia, and hypoxia, as well as monitor the effects of treatment with drugs such as anticonvulsants, sedatives, and anesthetics. The brain monitoring system will include easy-to-use disposable electrode arrays to be placed on patients by nursing staff with minimal training.

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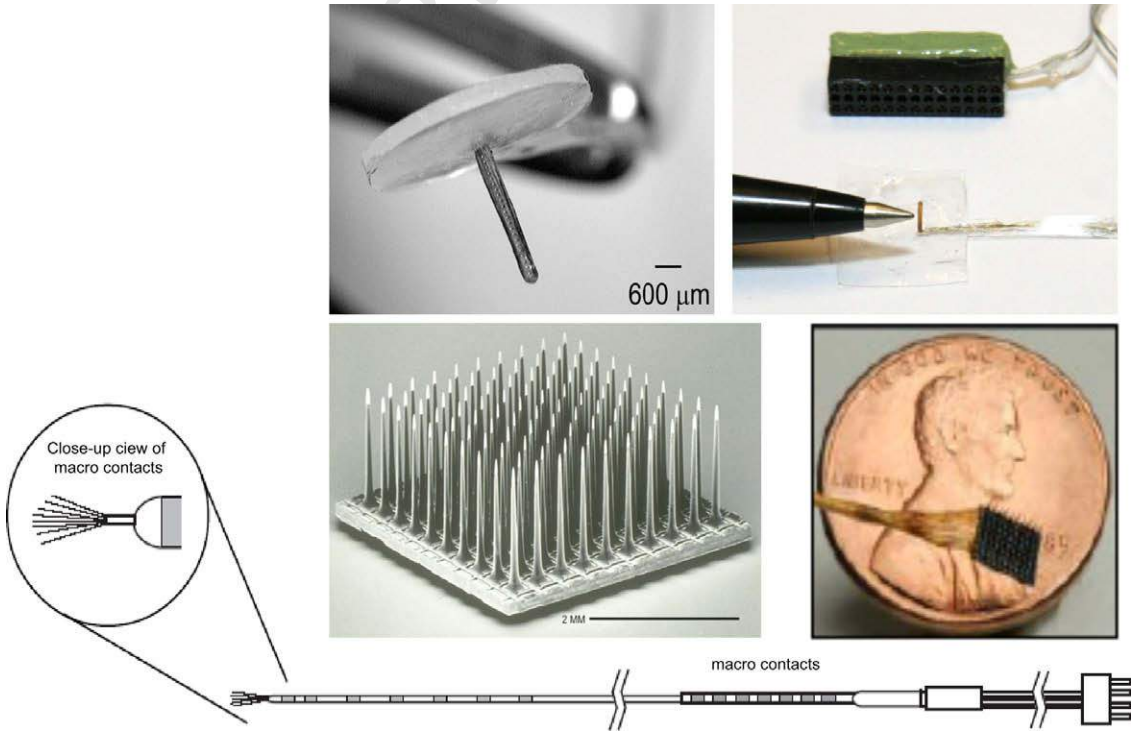

Fig. 14. Microelectrode arrays. Top, laminar microelectrode array [8]. Middle, NeuroPort system [6,7]. Bottom, Adtech microwire array.

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2.4. Microelectrode recordings in seizure localization, detection, and prediction

Sydney S. Cash

Approximately 30% of patients with epilepsy continue to have seizures despite maximal medical management [1–4]. Surgery may reduce or even eliminate seizures, but often requires intensive, invasive investigation to determine where seizures originate. Techniques that more precisely delineate the seizure onset zone may improve the outcomes of these surgeries. In addition, patients report that the uncertainty of the next seizure is one of the most debilitating aspects of the disease [5]. Robust detection and prediction of seizure onset could therefore significantly improve the treatment of epilepsy.

To date, procedures for seizure localization, detection, and prediction have relied on the EEG. Although powerful, such recordings represent the aggregate synaptic activity of millions of neurons. To better understand the physiological basis of the epileptogenic zone, as well as move toward new methods of seizure detection and prediction, we employed various microelectrode

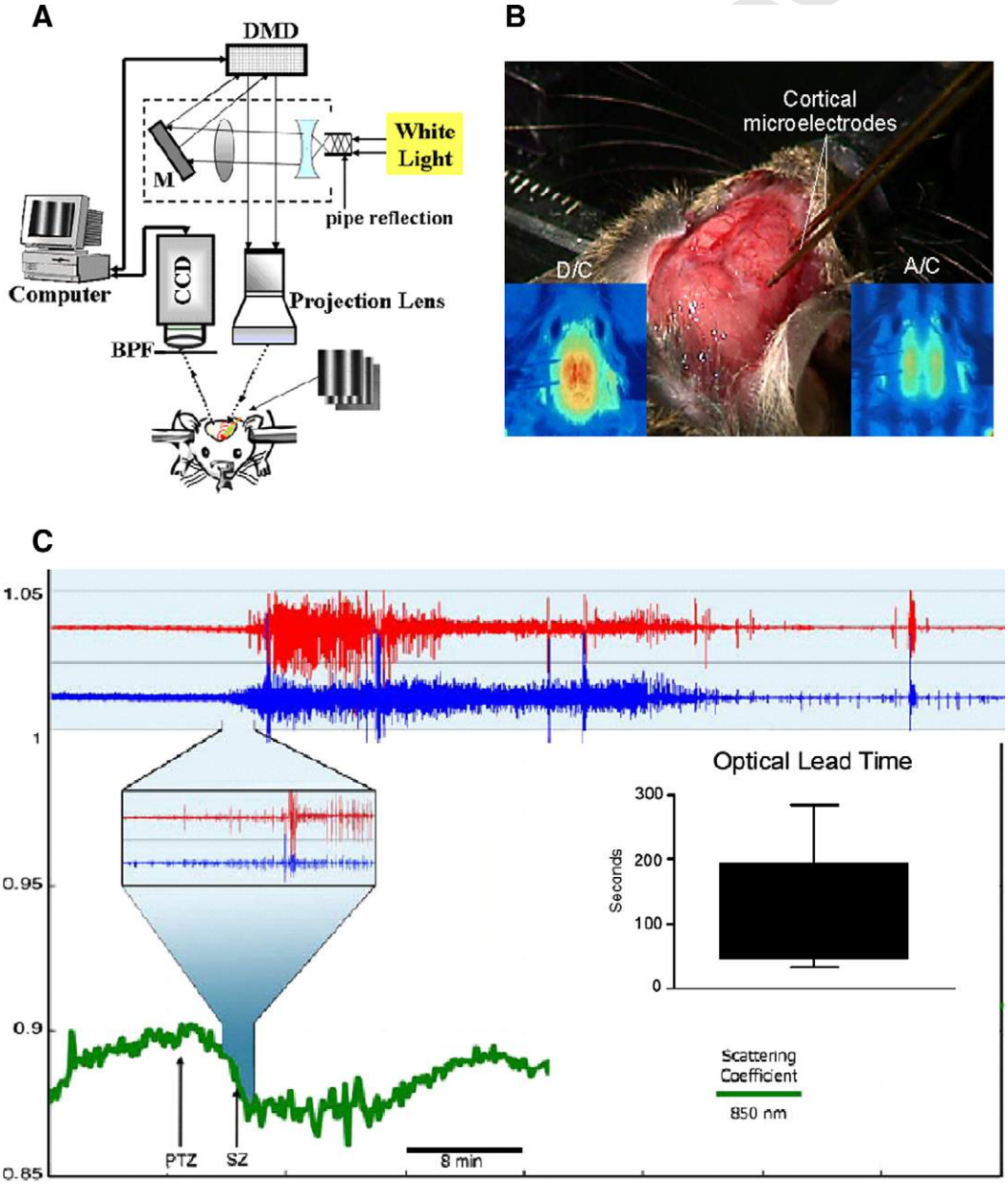

Fig. 15. (A) Modulated imaging (MI) system. CCD, charge-cooled device. DMD, digital micromirror device. BPF, bandpass filter. M, mirror. (B) The MI system is combined with EEG cortical microelectrode recording. Insets: Representative D/C and A/C modulated images generated by imaging with spatially modulated incident light. (C) Electroencephalographic recordings and optical scattering measurements following systemic administration of the convulsant pentylenetetrazol (PTZ). The optical scattering coefficient is derived using the MI system. Note synchronized seizure onset (SZ) in two separate cortical electrodes (red and blue) at a defined latency following PTZ injection. Prior to electroencephalographic seizure onset, there is a clear reduction in optical scattering at 850 nm (green), optically identifying the "preseizure state." Inset: Optical lead time defined as time at optical "trigger" (2SD change in optical scattering from baseline) to time of EEG seizure onset. Mean optical lead time was 118 s (range: 33–284).

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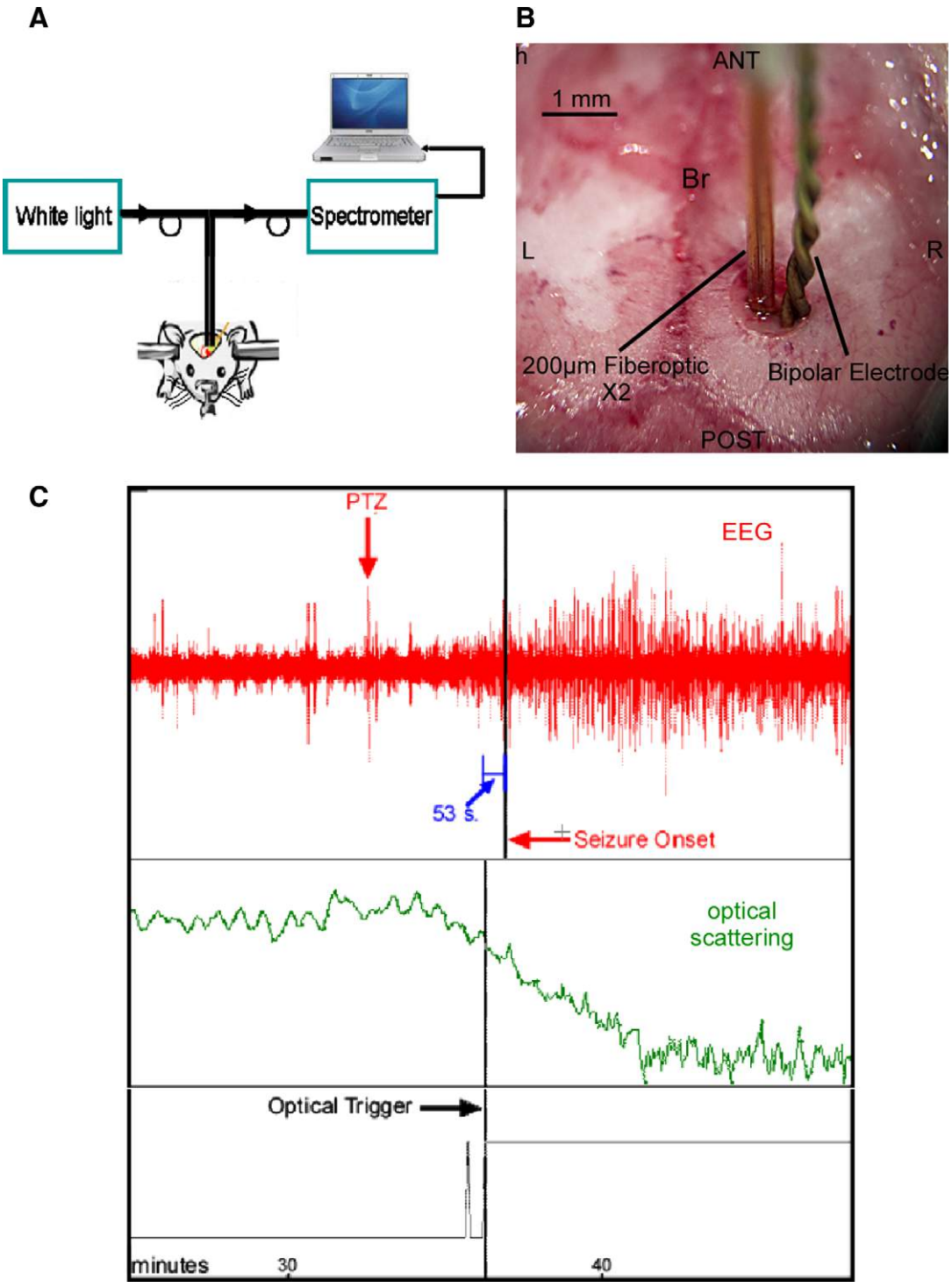

Fig. 16. (A) Broadband optical spectroscopy in vivo. (B) Dual fiberoptic (source/detector) stereotactically co-implanted into mouse hippocampus with bipolar EEG recording electrode. Concurrent EEG and optical recordings are then obtained from the in vivo hippocampus. (C) Example of fiberoptic seizure detection. Optical trigger occurs ~53 s prior to EEG seizure onset.

systems to record localized field potentials, the action potential firing of small neuronal ensembles and single neurons (Fig. 14). Higher-frequency activity, more localized synaptic activity, and the direct output of neurons are available with these techniques and have led to new insights into the mechanisms of seizure initiation and propagation and the physiology that defines the epileptogenic zone.

The layer of cortical activation during interictal and ictal discharges is dependent on its spatial relation to the seizure focus and propagation pattern of the seizure. Initial results using laminar arrays of microelectrodes point to at least two distinct patterns of columnar involvement during interictal discharges [8]. The first pattern, found within the seizure focus, consists of an early current sink in layer V with increases in multi-unit firing in layers V and VI.

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In contrast, further from the seizure focus, middle and upper cortical layers are more active.

Furthermore, preliminary analysis of ictal activity in 10 patients supports a temporal progression toward involvement of deeper cortical layers as the seizure progresses. This is most pronounced in recordings made outside of the region of seizure initiation as seen on corticography. In this region, early ictal discharges involve sinks in cortical layers near the surface. As the seizure continues, the current sinks become progressively deeper. This may reflect, at least in part, excitation of synapses on more proximal portions of the dendrite and a consequent increase in action potentials in the neurons constituting layers IV, V, and even VI, reflected in a large increase in local multi-unit firing.

In essence, there is a stereotyped differential involvement of specific cortical layers during interictal and ictal discharges that depends on their location relative to seizure onset as well as the stage of ictogenesis. These results directly support a primary hypothesis that the laminar pattern of activity, and therefore underlying physiology, differes depending on whether the discharge was recorded inside or outside the seizure focus. Thus, microphysiological recordings may improve the precision and, it is hoped, the success rate of resective epilepsy surgery.

Neuronal firing increases in advance of the seizure, suggesting new seizure prediction methods. We have performed simultaneous ictal EEG and laminar microelectrode array recordings in eight patients with intractable focal epilepsy (five males, ages 10–43) and analyzed the period preceding 15 seizures and 28 control blocks. Arrays were inserted near the seizure focus (as subsequently determined with ictal EEG) in temporal or frontal cortex, though not all electrodes were within or even next to cortex from which the seizure started. The potential gradient and multi-unit activity during a preictal period 30 min prior to the first ictal EEG change was analyzed in the spectral domain. For the potential gradient, no significant changes in broadband or band related spectral content (from 1 to 100 Hz) were observed during the preictal period. In contrast, multi-unit activity significantly increased (>2SD) in 7 of the 15 seizures (46.7%, six of eight subjects) compared with a baseline period taken during the first 100 s of an epoch. The onset of this increase was highly variable within and between subjects; in some instances the increase was only tens of seconds before the onset, and in others it was tens of minutes. In contrast, we found significant MUA increases, again compared with an initial baseline epoch, in only 4 of 28 control blocks (14.3%), yielding a sensitivity of 47.9% and a specificity of 80.7%. Using only data from the lower cortical layers significantly improved our sensitivity to 77% ($P < 0.05$, McNemar's test). Similar increases were observed in recordings from an additional patient using the NeuroPort array system. These data support a hypothesis that neuronal firing may increase significantly before the seizure is apparent on EEG. This correlates with data from animal models [9]. Multi-unit neuronal recordings may thus provide an entirely novel approach for seizure detection and prediction.

While still in the early stages, these novel techniques for recording microphysiological information from human cortex are already permitting a new view of epileptogenesis. Not only do they provide new physiological information but they may also lead directly to new methods of therapy.

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2.5. Optical detection of the pre-seizure state

Devin K. Binder

Clinical management of epilepsy is limited by the ability to both detect and treat seizures. As seizures are intermittent in patients with epilepsy, detection of seizures before they occur would be revolutionary in both warning patients and also developing "closed-loop" seizure detection and termination paradigms. The NIH Curing Epilepsy 2000 and Curing Epilepsy 2007 conferences have designated the creation of an effective closed-loop seizure detection/termination device as a critical benchmark in epilepsy research. The most important application would be to detect a focal seizure before it can generalize to involve the entire brain, and couple this detection to any of a variety of seizure termination methods. To date, seizure detection algorithms have been based solely on analysis of either surface or intracranial EEGs [1].

Our work has focused on a different approach—detecting physiological changes that occur prior to EEG seizure onset. Seizures are associated with depolarization of neurons and glial cells and concomitant ion flux and water movement from the extracellular space (ECS) to the intracellular space (ICS). This depolarization of small neuronal populations occurs prior to recruitment of enough neurons to generate a true "clinical" seizure detectable by EEG. Detection of water movement associated with early depolarization thus offers the potential for a sensitive method for detecting seizures. Indeed, our studies using cortical fluorescence recovery after photobleaching (cFRAP) have shown that constriction of the ECS occurs prior to electrographic seizure onset in a mouse model of generalized seizures [2]. Similarly, others have demonstrated preictal tissue impedance changes in vitro [3] and in vivo [4,5].

Recently, we have confirmed that there are optical changes in the brain that occur prior to seizure onset. Specifically, using spatially modulated near-infrared (NIR) illumination ("modulated imaging" (MI), developed at the Beckman Laser Institute at UCI [6]) with concurrent real-time video/EEG recording, we have demonstrated a reduction in optical scattering coefficient in well-defined mouse models prior to EEG seizure onset (Fig. 15). Our goals are to: (1) further define the optical characteristics of the preseizure state; (2) validate these findings in distinct seizure models; (3) develop a new miniature microfiberoptic NIR probe to detect preictal optical changes in deep brain structures (Fig. 16); and (4)

create an optical algorithm to predict seizures before they occur. If successful, this work will lead to a reliable, minimally invasive optical seizure detection algorithm, which could then be coupled to any of a variety of seizure termination methods in a "closed-loop" manner to terminate seizures before they become clinically apparent. Such a system would have direct benefit for the many patients whose seizures are currently unpredictable and uncontrolled by medications or surgery.

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Table 1

Challenges	Solutions (key technical components of the simultaneous EEG and DOI)
Interferences from scalp, skull and systemic physiology	Adaptive filtering for interferences cancellation [6,7]
Inefficient imaging algorithm	Multi-modality imaging algorithm using simultaneous EEG and DOI [8]
Poor knowledge of optical signature of seizure	Simultaneous EEG and optical detection of hemodynamics and neuronal activity [9]

2.6. Simultaneous EEG and diffuse optical imaging to improve noninvasive localization of epilepsy

Quan Zhang, Andrew J. Cole, Sydney S. Cash, Andrei V. Medvedev, Gary E. Strangman

There are more than five million patients with epilepsy worldwide who are potential candidates for surgery. Identification of surgical candidates often consists of intracranial EEG recordings, which requires implantation of subdural or depth electrodes and carries a risk of significant complications including infection, stroke, and death. Reducing the need for an invasive evaluation would thus have significant clinical impact [1].

Diffuse optical imaging (DOI) is a promising tool complementary to existing noninvasive presurgical evaluation. DOI has good specificity (direct measurement of cerebral hemodynamics) and temporal resolution; further, it is noninvasive, nonionizing, and low cost. Unlike EEG mapping, DOI does not have the volume conductor problem and is thus spatially more confined and specific. In addition, it can be developed into a portable device, such as our OpticHolter (patent pending), and used for long-term and ambulatory monitoring to record multiple seizure events, rather than snapshots as one obtains from other imaging modalities such as MRI. DOI probes the head 2 to 3 cm down from the scalp, and provides a functional image with about 5-mm resolution. The disadvantage of DOI is that it is sensitive to global interference such as that from scalp and skull. In recent years, several studies have shown that it is possible to use noninvasive optical methods to detect hemodynamic changes associated with seizures and very preliminarily map their location [2–4]. Thus far, the detection and mapping quality is not satisfactory, with occasional contradictory results [5]. The challenges are summarized in the first column of Table 1.

With simultaneous EEG and DOI we may be able to improve our ability to localize the epileptogenic focus, consequently reducing risk to patients as well as cost. Three key technical components of simultaneous EEG and DOI, or potential solutions to the current challenges, are listed in the second column of Table 1. We have acquired preliminary results to demonstrate the effectiveness of each component. For example, our recent studies have shown that 66% of optical oxyhemoglobin measurements exhibited substantial systemic interference (e.g., from scalp and skull),

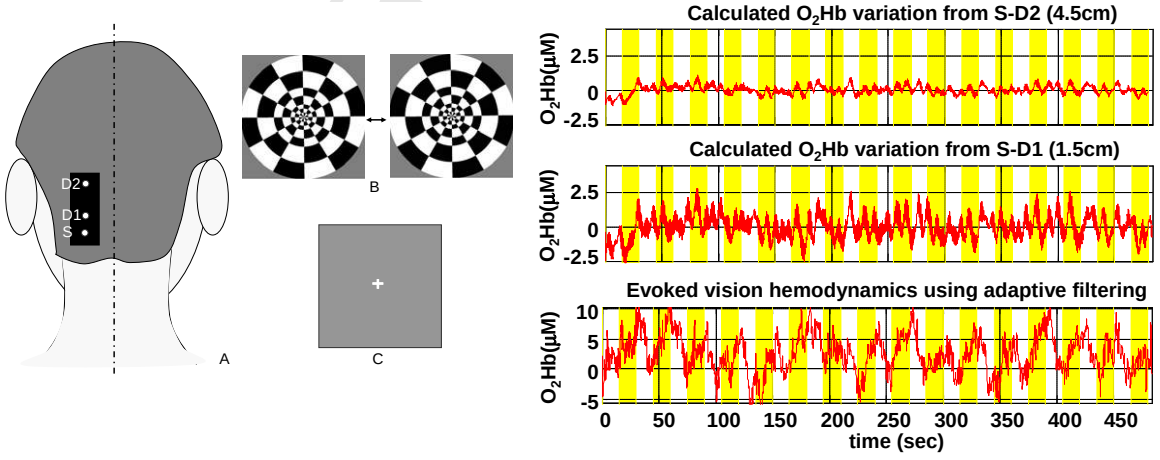

Fig. 17. An example of detecting evoked visual hemodynamic responses in a human subject as a demonstration of the novel global interference cancellation technology. (A) Probe configuration for the vision test. (B) Vision stimulation: alternating counter-phased radial checkerboard. (C) Rest period: uniform field with a central fixation cross. The first row of the time series is the target O_2Hb measurements from S-D2 with 4.5 cm source-detector separation. Although the target dataset was expected to contain an increase in O_2Hb following stimulus onset (and concomitant decrease following stimulus offset), the raw time series does not show any obvious expected signal change. The second row is the reference measurements from S-D1 with 1.5 cm source-detector separation. The fact that the signal variations in the target O_2Hb closely match those of the reference O_2Hb (which should contain no visual response) suggested that indeed global interference may dominate the target dataset. The last row is the adaptive filtering result for the target measurement (also with sensitivity correction to cancel the partial volume effect). We see that after adaptive filtering the interference is substantially reduced, and the expected increase following stimulation onset and return to baseline during rest periods are clearly shown. The temporal changes are appropriately associated with the stimulation paradigm.

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and 71% of these cases showed CNR improvement after our novel and published adaptive filtering approach. A typical case demonstrating the effectiveness of the adaptive filtering approach is shown in Fig. 17.

In addition, our simultaneous EEG and DOI results show that the optical method is sensitive to not only cerebral hemodynamics but also neuronal activity, which can potentially help seizure detection [9]. Lastly, we have demonstrated with our publications and patents that improved image quality can be acquired by multimodality imaging, through image reconstruction and spatial regularization [8].

Our next step is to recruit eight inpatients with focal epilepsy who are, for clinical reasons, undergoing long-term video/EEG monitoring for the simultaneous EEG and DOI study. We will compare the CNR before and after our adaptive filtering approach, and preliminarily test its sensitivity and specificity for the improvement for seizure detection and localization compared with conventional techniques. With our portable ambulatory NIRS technology, we are also looking into the possibility of ambulatory optical monitoring for epilepsy care [10].

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3. Intracranial treatment systems

3.1. Overview

Steven Schiff

What is a seizure? That is, dynamically, what is the definition of this phenomenon? If one were to look at the components of the brain, such as neurons and, for the adventurous, glia, microvasculature, and extracellular space as well, how do the interactions between these elements create seizures? We have countless bits of pieces of information regarding these questions. But we do not know the answers.

In this section on intracranial treatment systems, a variety of cutting edge projects are discussed: computational models of seizures, the use of hybrid materials for implants, drug delivery directly into brain, seizure prediction, and a variety of intelligent feedback systems. Yet despite the cutting edge nature of the technical advances discussed, there seems a deeper gulf between the science and medicine for the intracranial treatment of seizures, and for instance, the comparable state of our knowledge for infectious diseases or diabetes.

Why? The obvious answer from most is that the complexity of the brain is far beyond the complexity of single-cell microorganisms or glucose regulation. But host interaction with microorganisms and endocrine pathways are also highly complex systems. We are all brain complexity chauvinists, yet there seem several aspects of intracranial device implementation for which further articulation of the problem, and defining unmet needs, is a useful exercise.

Although seizures are symptoms of the disease epilepsy, any clinician who has observed large numbers of patients with epilepsy during their seizures and their associated EEG recordings recognizes that there are a wide variety of seizure classes and, within each class, a wide variety of variation in these patterns. Would anyone building a device to control a machine that gave the output of, say, an absence seizure, think that the same design could control a generalized tonic–clonic seizure? But we treat epileptic seizures as if they were a monolithic entity. The contrary assumption is a bit frightening of course—that for the dozens of seizure types, dozens of different types of intracranial treatment systems might be necessary. If we change the wording of the previous sentence to use drugs instead of intracranial treatment systems, it would not be controversial. Perhaps it is likely that the biomedical community has been very naïve in their expectations for intracranial systems—that different types of seizures will require customized designs and strategies.

We are probably now close to if not beyond the 100,000 mark for intracranial stimulation systems implanted in patients worldwide for a variety of conditions, of which epilepsy is a small but growing fraction. Yet the vast majority of our electrode materials are stainless-steel and occasionally platinum alloys. We have done little work toward improving the electrical characteristics of sensing and stimulation electrodes for human use, although there are numerous advances in materials science that can serve us well for such applications. Much of our electrical stimulation strategy for seizures is a direct outgrowth of previous electrical strategies for cardiac and, more recently, Parkinson's disease applications. We know very little about the electrical interaction of electrical currents and the epileptic brain, certainly not at a detailed cellular interaction level. We also have very little information regarding the degenerative effects of electrode implantation into humans, nor the long-term effects of chronic electrical stimulation. We market stimulators for human use that permit voltages that exceed the water window for hydrolysis of water by nearly an order of magnitude, and we have never defined the implantation toxicity baseline from which an adequate assessment of chronic electrical toxicity can be properly evaluated. Most of these open issues are scientifically "low hanging fruit" for the people involved with research and development of intracranial systems, and pursuing them will lead to near-term practical improvements for patients with seizures.

No engineer would design a control system for a complex device, such as a space craft, an airplane autolander, or a nuclear power plant, without a mechanistic computational model of that device through which to perform model-based control. But all of our efforts to control epilepsy have used model-free empirical ap-

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proaches to feedback control. As a community we must seem optimistic that we might get lucky with such strategies. But we push vigorously forward in the face of the overwhelming basic science and clinical experience which so far does not lend tremendous encouragement to this approach. Nevertheless, the basic science and technologies required for us to create mechanistic models based on the microscopic interactions of the cellular and ionic dynamics that create macroscopic seizures are now very much within our reach. Once we do this, model-based control is a sophisticated and mature field waiting for us to create the interdisciplinary bridges to bring it to epilepsy applications. Control theory tells us that we cannot lose; such approaches are valuable because they *are* the optimal strategies to observe and control dynamical systems.

Similarly, the microfluidics that underlie treatment strategies such as convection-enhanced drug delivery are now increasingly tractable given presently available optical measurement and computational techniques. Combined with detailed studies of the geometry of the spaces through which such compounds are driven by bulk flow and diffusion for a given part of the brain, more effective drug delivery strategies can be designed.

The confluence of our advances in science, engineering, and medicine all now put in place a set of skills and tools that stand ready to elevate intracranial device therapy to a viable alternative to conventional pharmacological and resective approaches to the treatment of seizures. Perhaps the most difficult unmet medical need for such strategies is inherent in the social difficulties of bridging the scientific and medical disciplines required to exploit the available technologies for the complexities of controlling epilepsy. The presentations in this section all point to strong ongoing efforts to make those bridges.

3.2. What can we learn about learning, and how does this relate to epilepsy?

David Hsu, Murielle Hsu, John M. Beggs

Electrical stimulation of the brain, either via the vagus nerve or with intracranial electrodes, is an attractive approach to the treatment of epilepsy. However, current vagus nerve stimulation protocols produce only a modest improvement in seizure control, with fewer than 10% of patients becoming seizure free [1,2]. Preliminary reports on devices using intracranial stimulation suggest a similarly modest effect. The major stumbling block is that the mechanism by which electrical stimulation works is unknown, and so it is not possible to design better stimulation protocols in an intelligent way.

We have approached this problem by considering first one of the most important normal functions of the brain, which is to learn. We have proposed that learning and epileptogenesis are intimately related, and that epileptogenesis may involve the learning and "burning into memory" of spatially hyperextended, temporally persistent patterns of neuronal activation [3]. These patterns are referred to as *seizure circuits*. Within this perspective, we suggest two new approaches to the design of electrical stimulation protocols for the treatment of epilepsy. We first review how the brain learns.

Learning in the brain is reflected by changes in the individual connection strengths between pairs of neurons. According to Hebb's rule, correlated firing between a pair of neurons results in a strengthening of the connection between them; that is, "neurons that fire together, wire together" [4]. This kind of learning is competitive, so that connections that are initially a little stronger than most other connections tend over time to become stronger and stronger, while those that are initially weaker than most others tend, over time, to become weaker and weaker. The result of applying simple Hebbian learning rules to computer models is nearly always catastrophic, with such models nearly always approaching either a state of continuous, runaway excitation or one of global silence [5].

Real brains of course avoid this catastrophe. As proposed by Marder and co-workers [6], there must be homeostatic mechanisms that maintain neuronal activity and connectivity within physiological ranges. At least two mechanisms have been found so far [7,8]. Furthermore, with respect to information transmission, processing, and storage capacity, it has been demonstrated that there is a unique level of connectivity at which brain performance is optimized [9–12]. For extracellular local field potentials (LFPs), this level of connectivity is most simply defined in terms of the branching ratio ($\acute{o}$), which gives the average number of locations at which LFP spikes occur in response to an LFP spike at any given single other location. The branching ratio is a measure of the efficacy of neuronal output. In terms of the branching ratio, optimal brain performance occurs at a branching ratio of $\acute{o} = 1$, which is referred to as *critical connectivity*. There are mathematical properties at critical connectivity that are of high theoretical interest [13–16], which we do not explore here. More pertinent to our purpose is the fact that, experimentally, the branching ratio hovers near critical connectivity over a wide variety of in vitro and in vivo systems [10,17–24]. Given the importance of critical connectivity to brain learning, this result is not surprising. It is evolutionarily advantageous for brains to maintain connectivity near criticality. Brains that cannot do this do not work as well and are at risk for catastrophic malfunction. This conclusion holds for any Hebbian learning system, and does not depend on the biomolecular details of how learning takes place.

We have performed stability analysis on a simple computer model of a continuously active neural learning system. We found that homeostasis of activity and critical connectivity are independent, separate constraints [25]. For a neural system to stay near criticality, it is a necessary condition that neural activity be regulated predominantly by scaling the spontaneous activity of individual neurons, while neural connectivity is regulated predominantly by scaling connectivity-related (or "stimulated") activity. Spontaneous activity refers to neuronal discharges that do not depend on preceding neuronal discharges elsewhere. Stimulated activity refers to neuronal discharges in response to input from other neurons. These two conditions of stability are general and do not depend on the details of the underlying biomolecular mechanisms. We discussed other conditions of stability in our prior study [25].

The distinction between spontaneous and stimulated activity is key. If, for whatever reason, there is a drop in spontaneous activity, then stimulated activity tends to increase, in partial compensation. If there is an increase in spontaneous activity, then stimulated activity tends to decrease. An increase in overall stimulated activity implies strengthened functional connectivity. If the level of connectivity rises above critical levels (to *supercritical* levels), then the system tends to produce activation patterns that are spatially hyperextended. Furthermore, if supercritical connectivity is maintained for a prolonged period, then the system learns and burns into memory some of these spatially hyperextended states. If spatially hyperextended states are burned into memory, then they may be reactivated at some random time in the future. Reactivation of such spatially hyperextended states then sets the stage for a seizure. Thus, prolonged supercritical states are epileptogenic.

How might prolonged supercritical states arise? From computer simulations, we have shown that they may arise after status epilepticus and after acute deafferentation, because these insults produce states of suppressed spontaneous activity which then trigger compensatory supercritical connectivity [3]. Acute deafferentation is a model for traumatic brain injury. Thus, it would be desirable to detect whenever the brain connectivity rises to supercritical levels, and to intervene to bring connectivity back down to near-critical levels.

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How might one bring connectivity levels back down? One possibility is to stimulate the brain electrically in such a way as to boost spontaneous activity without boosting connectivity-related activity. The rationale is that boosting spontaneous activity should homeostatically allow connectivity levels to drop. The stimulation may be given chronically either through the vagus nerve or through intracranial electrodes. One may try frequencies in the range 40–150 Hz, because these frequencies are known to be excitatory. Care must be taken not to stimulate the brain in exactly the same way each time a train of electrical pulses is delivered, lest one teach the brain a new seizure circuit, through a mechanism akin to kindling. With vagus nerve stimulation, one may try randomizing the frequency of stimulation, that is, delivering one train at a randomly chosen frequency between 40 and 150 Hz, and then the next train at a different frequency chosen randomly from the same range. If intracranial electrodes are used, there is the additional option of randomizing which electrode is used to stimulate at which frequency.

Of course, the effect of such electrical stimulation must be monitored to know if the brain is near criticality, above it, or below it. The goal, for optimal suppression of seizures and for optimal brain performance, is to achieve critical connectivity. However, how to measure connectivity in vivo relative to critical connectivity may not be trivial. For instance, LFP spikes can trigger LFP spikes elsewhere on at least two time scales. There is a fast response, occurring between 4 and 40 ms after the initiating spike, but there can also be a slower response at 100–250 ms later. Disentangling cause and effect relationships to calculate a branching ratio in such a system can be a formidable theoretical challenge [3].

The presence of at least two time scales in LFP response times has significance in the theory of learning. It may be that the faster "gamma" range response serves to bind spatial patterns, whereas the slower "theta" range response serves to link one spatial pattern to the next. Such a scheme has been proposed by Lisman [26]. Gamma binding of spatial patterns is necessary for static memory, for instance, the instantaneous recognition of the letters of the alphabet or of faces. Theta linking of spatial patterns is necessary for higher cognitive tasks, such as learning the melody of a song, reading a novel, or watching a movie.

The existence of theta temporal linking also has significance for epileptogenesis. A seizure represents not simply neuronal hyperactivity or even neuronal hyperactivity plus supercritical connectivity. A seizure is also characterized by stereotyped electrical discharges that recur in time for an abnormally long period. In the context of gamma binding and theta linking, a seizure circuit can be thought of as a spatiotemporal sequence that comes back on itself, a recurrent loop from which the brain cannot easily exit. The formation of such a loop represents a third necessary condition for epileptogenesis [3].

A key point here is that a seizure circuit has to be learned. If a seizure circuit is learned, then it should be possible to *unlearn* it. If learning a seizure circuit involves gamma binding and theta linking, then one may imagine using the same mechanisms to "overwrite" pathological circuits. For instance, every time a seizure circuit is activated, one may inject trains of spatially random electrical stimulation patterns into the brain, with each spatial pattern delivered in a gamma frequency burst and the bursts separated at theta intervals. The brain will then "see" a corrupted version of the seizure circuit. It is thought that memory traces must be reactivated intermittently to maintain them. If every or nearly every reactivation of a particular seizure circuit is corrupted by the injection of random gamma–theta trains, then eventually the brain should "forget" that particular memory trace. In this way, it may be possible to *erase* seizure circuits in a selective way and, in effect, to reverse epileptogenesis.

In trying to erase seizure circuits with vagus nerve stimulation, gamma–theta trains could be delivered only during activations of a seizure circuit and with the frequency of the gamma component chosen randomly, different with each gamma burst. By randomizing the frequency of the gamma burst, it is hoped that the spatial projections of the vagus nerve onto the cortex are also randomized. Whether spatial randomization occurs at the level of the cortex will have to be experimentally verified. As mentioned above, with intracranial electrodes, there is the additional option of randomizing which electrode is used to stimulate at which frequency, so as to be certain that the spatial projection is random. Care must be taken, as before, not to teach the brain new seizure circuits by injecting patterns with hidden recurrences and to deliver such randomizing stimulations only during activations of pathological circuits, so that normal cognitive processes are not erased.

In summary, we propose that epileptogenesis involves the learning of pathological seizure circuits. Any animal that is capable of learning is also capable of developing epilepsy. Certain biomolecular substrates and certain external provocations may increase the risk of epileptogenesis, but the learning and burning into memory of seizure circuits is a common final pathway. If it proves possible to maintain brain connectivity chronically at near-critical levels, then it should be possible to suppress epileptogenesis. If it proves possible to inject random gamma–theta trains into every activation of a particular seizure circuit, then it should be possible to erase seizure circuits selectively and, in effect, to cure epilepsy.

Acknowledgments. D.H. was supported by a grant from the National Institutes of Health (1KL2RR025012-01). J.M.B. was supported by a grant from the National Science Foundation.

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3.3. Hybrid cell silicon neural implants for closed-loop seizure therapy

Jenna Rickus, Pedro Irazoqui

Despite a growing number of antiepileptic drugs, seizures in at least 30% of patients with epilepsy remain pharmacoresistant [1, 2]. Many of the effective drugs have severe or intolerable side effects. Although the specific mechanisms of drug resistance remain unclear, poor targeting of orally ingested drugs to specific brain regions, reduced drug concentration at target sites by multidrug transporters, and adaptation to continuous drug exposure are likely culprits [3]. Poor or improper spatial targeting is also a significant cause of unwanted side effects [4]. Spatial and temporal targeting of drug action to specific brain regions immediately prior to and during seizure onset could represent a significant advancement in the ability to stop seizures without side effects. A recent study revealed that of 246 patients with drug-refractory epilepsy, ~80% had focal or partial epilepsy [5], indicating that many patients are potential candidates for local therapy.

The 2000 NIH Curing Epilepsy Conference resulted in a specific research benchmark to "successfully use a biosensor device (comprised of a biodetector, mini-pump, microstimulator, or other detector systems) that reliably anticipates or identifies seizures, and applies targeted treatment to abort seizures in at least one form of epilepsy." The existing engineering response to this challenge is the application of traditional devices with electrical, mechanical, and chemical components [6, 7]. Closed-loop electrical stimulation is promising but unproven, and the mechanism of action remains elusive [8–13]. Implanted drug pumps provide temporal and spatial delivery, but the problem of a chronic drug reservoir is a challenge. The biological approach, cell transplantation of biomolecule-releasing cells, provides spatial delivery of drug, but cannot yet provide seizure-triggered control of release on the time scale of seconds. With no specific control mechanism to respond to seizure triggers, treatment resistance and side effects may continue to be a problem. Hybrid cell silicon devices combine these approaches by integrating exogenous cells as a drug/neurotransmitter source with a closed-loop electrical device to provide controllable chemical delivery with a chronic chemical source. In addition, advances in device hardware and circuitry are needed to implement advanced prediction, detection, and treatment delivery for closed-loop therapies in general.

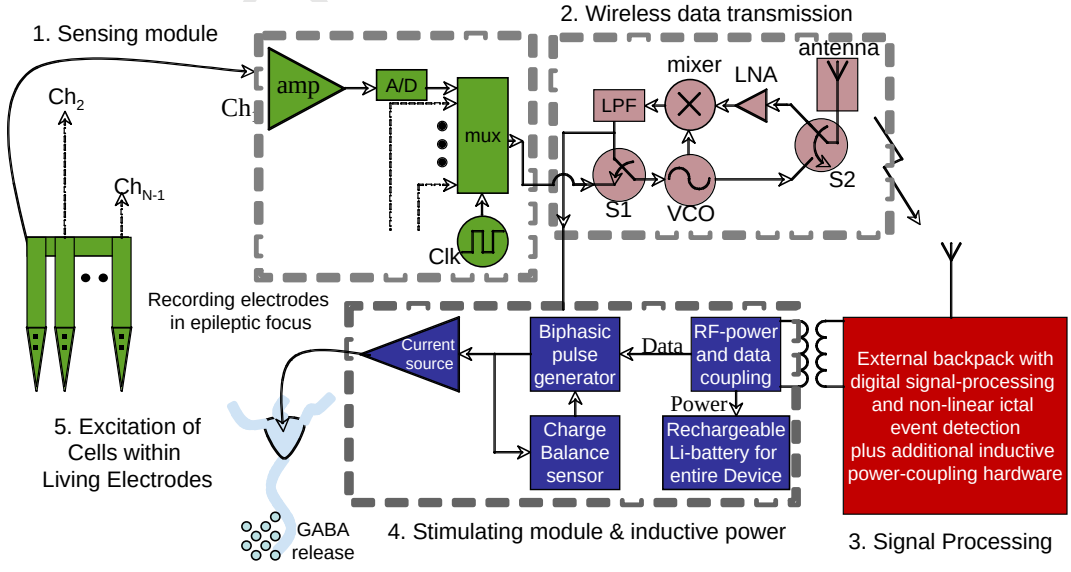

Fig. 18. A closed-loop living electrode prosthetic for epilepsy.

Please cite this article in press as: Schachter SC et al. Advances in the Application of Technology to Epilepsy: The CIMIT/NIO Epilepsy Innovation Summit Epilepsy Behav (2009), doi:10.1016/j.yebeh.2009.06.028

The overall objective of this work is to establish hybrid cell silicon implants as an in vivo therapeutic intervention for neural inhibition of epileptic foci, while implementing next-generation device components. This first prototype hybrid device is presented here (Fig. 18). This device integrates inhibitory neural cells with stimulating electrodes using sol–gel biocomposite materials as an interface. The cells contribute neurotransmitter production and release, while the electrodes provide a temporal trigger and integration into computer-driven control systems. We have established in vitro feasibility for calibrated GABA release, and designed, built, and tested a 54,000-transistor prototype chip (Fig. 19) containing the recording, telemetry, stimulation, and power modules.

The rationale to focus on a GABAergic hybrid device for the first prototype was based on both microinjection and cell transplantation studies. Microinjections of the GABA agonist muscimol into anatomical locations important in seizure generation or propagation can inhibit seizures or secondary generalization of seizures in several different animal models [14–16]. Transplantation of GABA-rich fetal grafts showed mild reduction of seizure parameters, but was challenged by the heterogeneity of the grafts [17, 18]. Clonal lines of immortalized cells expressing the GABA-producing enzyme GAD [19, 20] have also shown mild reduction of seizure parameters [20–25]. The microinjection studies show that seizure inhibition by GABAergic inhibition is possible. The cell transplantation studies show that cell-based GABA therapies are promising but currently suboptimal, as they have not yet been able to achieve the same level of protection as the direct microinjection of agonists. Hybrid cell silicon devices that control and boost GABA release could potentially bridge this gap.

We have designed, fabricated, and tested a custom, low-power, application-specific integrated circuit (ASIC) to drive biphasic, charge-balanced current pulses. In addition, the microchip has sensing, telemetry, and powering capabilities. The ASIC records and transmits in vivo neural signals from untethered rodents and simultaneously stimulates biological tissue. The device designs share a common subset of modules. The work described here forms a proven starting point for next-generation modules that are currently under development. The existing chip combines modules for sensing biological signals, stimulating a cellular or system response, telemetry (transmitting and receiving data), and powering an implantable systems of modules. These modules were fabricated through the MOSIS service (http://www.mosis.org/).

Our new sensing design uses chopper stabilization to greatly reduce noise effects, allowing higher fidelity in monitoring the activity of cells. Additional savings in power consumption allow us to greatly increase the number of channels that can be monitored simultaneously. The new stimulating circuit has a high-output impedance to ensure current flow into engineered neurons, and is charge balanced, preventing induced cell death in chronic stimulating applications. The stimulator is capable of delivering constant current at any waveform, within the limits of the digital circuitry resolution, which is critical because the current features dramatically influence the neurotransmitter release properties. New telemetry designs increase the carrier frequency to 5.8 GHz, doubling the data rate and reducing antenna area by a factor of 4. Prior wireless designs are limited to 16 channels. Because of the higher carrier frequency, lower-power consumption, and on-board digitization, the new circuit has the capability of sensing and transmitting from 1024 channels simultaneously. The efficiency of the existing powering modules is approximately 25%. Next-generation devices in development have a predicted efficiency greater than 90%. A rectified voltage has been used to power implanted devices directly, but we use it in conjunction with a standard voltage regulator to recharge an implanted battery to drive the ASIC in the implant.

We have demonstrated the feasibility of calibrated GABA release by living (cell-coated) electrodes. The device stimulation module was coupled to two different cell populations: differentiated P19 cells and CN1.4-GAD65 cells. Although not candidates for therapeutic intervention, P19 embryonic carcinoma cells [26] are a well-studied cell model that can form mature neurons with polarity and functional synapses [27, 28]. Because P19 cells form both glutamatergic and GABAergic neurons, they will not be used for in vivo seizure prevention, but are a powerful model system for in vitro living electrode development because of their mature physiology. Immortalized embryonic cortical cells (CN1.4) that were further engineered to express the GABA-producing enzyme GAD65 [20, 29] were also used as an immature neural cell model.

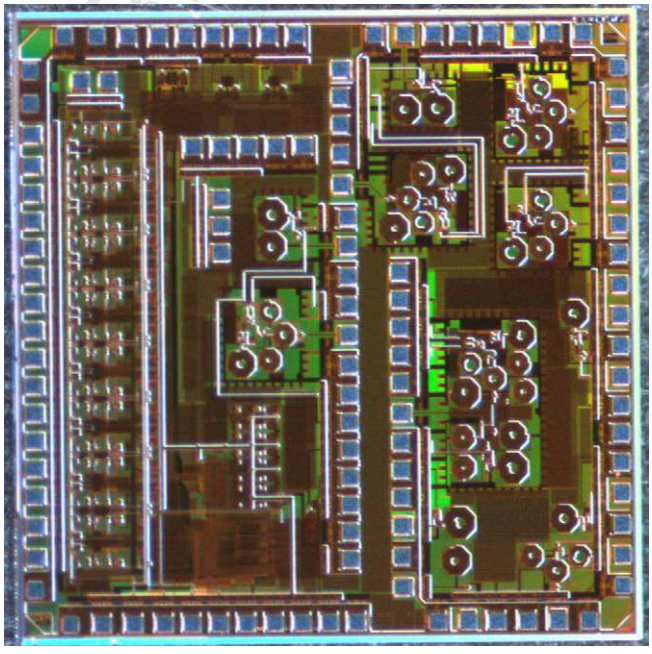

Fig. 19. Photograph of the fabricated 54,000 transistor microchip.The chip is roughly 4 × 4 mm.

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The CN1.4-GAD65 cells express high levels of GAD65, produce GABA, and reduce seizure parameters in rat seizure models [20, 21, 23, 24].

Neurotransmitter release was quantified by gas chromatography (GC)/mass spectrometry (MS). Glutamate and GABA release from the P19 cells was linearly related to stimulation current. The GABA release from engineered CN1.4-GAD65 neurons was not linear and required higher current amplitude to stimulate release. Little to no stimulated glutamate release was measured for the CN1.4-GAD65 cells, as expected. The difference in calibration curves is likely due to differences in release mechanisms between the mature neurons and immature neural cells. The stimulation frequency changes the slope and range of the effect of stimulation amplitude. Most importantly, stimulation increased neurotransmitter release approximately one order of magnitude compared with basal release, indicating a potential to have a greater impact on seizure parameter reduction on a per cell basis compared with unstimulated transplanted cells.

These results demonstrate that hybrid cell silicon devices for controlled neurotransmitter release are possible. The critical next steps must focus on efficacy for seizure inhibition and prevention. If efficacious, then the most prominent next challenge will be to identify the best cell source for human intervention.

Acknowledgments K. Thompson, A. Campagnoni, and A. Tobin generously supplied the CN1.4-GAD65 cells.

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3.4. Developing a subdural hybrid neuroprosthesis to treat intractable focal epilepsy

Nandor Ludvig, Hai M. Tang, Shirn L. Baptiste, Geza Medveczky, Jacqueline French, Werner K. Doyle, Chad Carlson, Ruben I. Kuzniecky, Orrin Devinsky

In 2004, building on our previous observations and inventions [1, 2] (U.S. Patent 6,497,699), we initiated a research program to

develop an implantable subdural hybrid neuroprosthesis (HNP) to treat intractable focal epilepsy. Here we provide a brief description of the device, the main results, and the challenges that lay ahead.

The first novel feature of this apparatus is that it uses localized AED delivery into the epileptogenic zone(s) for seizure control, instead of electrical stimulations employed by other neuroprostheses (e.g., RNS by NeuroPace). Second, the subdural HNP differs from tissue transplants or drug-releasing intracortical polymers because it also monitors the neural activity of the treated epileptogenic zone(s). Third, the apparatus delivers drugs specifically into the cerebral cortical epileptogenic zone(s) transmeningeally, via the subdural/subarachnoid space.

The feature of inhibiting focal seizure activity with feedback-controlled transmeningeal drug delivery permits the postimplantation testing of various AEDs and chemical compounds until the most efficient seizure-preventing drug solution is identified for the patient, and this selected drug solution can be flexibly modified later, during the course of HNP treatment, if necessary. Another advantage is that the device can deliver AEDs into large, multiple, neocortical epileptogenic zones without spatial restrictions and without using tissue-penetrating cannulas or catheters, as the HNP can accommodate several large-size drug delivery strips positioned in the subdural/subarachnoid space.

Because the subdural HNP is designed to deliver AEDs into stable neocortical epileptogenic zones identified in preimplantation recordings, patients with very widespread neocortical or unstable, shifting, or expanding neocortical epileptogenic zones may fail to respond to HNP treatment, especially if these zones are significantly influenced by subcortical seizure-triggering inputs. However, constructing a new generation of subdural HNPs, with the capability of turning on drug delivery at new subdural locations while turning off such delivery at other locations, and in some cases equipped with supplemental subcortical drug delivery fibers, might solve this problem. Also, the design of the subdural HNP is complex, with electrophysiological monitoring and drug delivery components. Complex biological and artificial systems may be prone to malfunctions.

Proof-of-concept studies

Rats.

In freely-moving rats, epidurally delivered (1) pentobarbital can prevent and terminate focal neocortical seizures induced by local acetylcholine (ACh) applications [3], (2) GABA can terminate such seizures but fails to prevent them [4], and (3) muscimol can prevent these focal seizures within 30 s of its epidural delivery in concentrations as low as 0.8 mM (Fig. 20A) [5].

Nonhuman primates.

Subdural/subarachnoid space-delivered muscimol prevented seizures in squirrel monkeys (*Saimiri sciureus*) [5].

Patients with epilepsy

In three patients with intractable focal epilepsy, placement of lidocaine-soaked Gelfoam onto the pia mater of the neocortical epileptognic zone before resective surgery significantly reduced the frequency of local epileptiform discharges [6].

Histological evidence for transmeningeal drug diffusion

In rats, water-soluble small molecules like *N*-methyl-D-aspartate (NMDA) readily cross the cerebral meninges, penetrate into the deep layers of neocortex, and remain within the exposed cerebral cortical region [7]. Transmeningeal drug diffusion can be facilitated by both increased drug concentration and increased hydrostatic pressure inside the drug delivery device.

Safety studies in nonhuman primates

Long-term (5- to 8-month) behavioral monitoring and neurological examinations on two squirrel monkeys implanted with a subdural drug delivery device placed over the right motor cortex revealed no neurological symptoms or deficit; the monkeys' behavior was indistinguishable from normal [5].

Development of the HNP hardware

The architecture of the subdural HNP (U.S. Patent Application 20070060973) includes six components: (1) the subdural electrode–drug delivery strip(s), (2) a signal conditioner embedded in the cranial bones and connected to the rest of the apparatus via tunneled wires and tubing, (3) a microprocessor for both seizure prediction/detection and hardware control, (4) a two-way radiofrequency communication module for postimplantation software adjustment and emergency signaling, (5) a dual peristaltic minipump [8] (Fig. 20B), refillable through the skin, for both delivering drugs and regularly flushing the subdural drug delivery strip(s), and (6) a transcutaneously rechargeable power supply. Most of these components, including the minipump (Fig. 20B), were constructed and tested by us, although are not yet integrated in a single device.

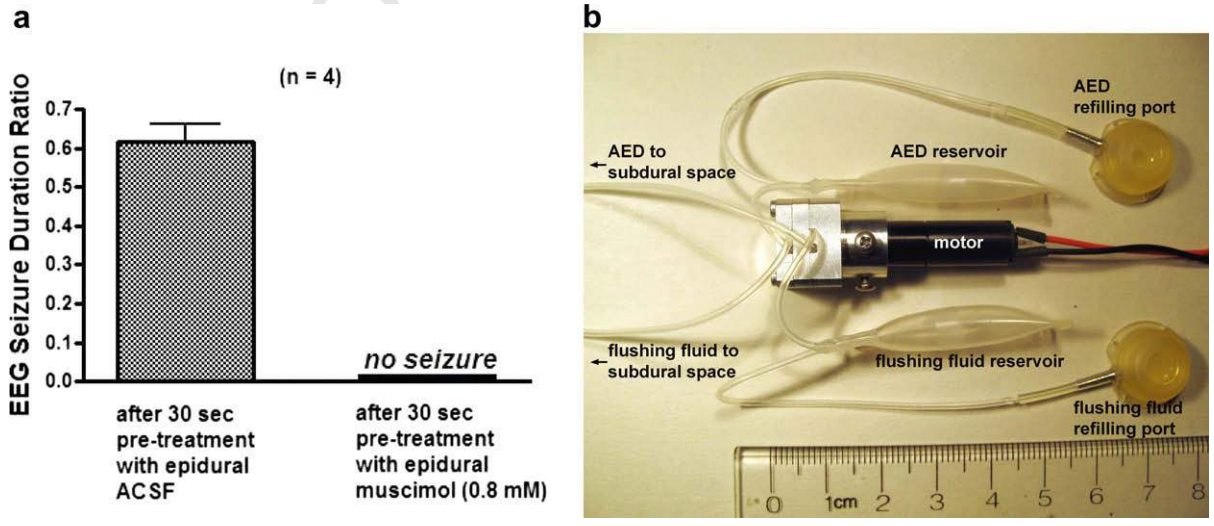

Fig. 20. (a) Statistics of the focal seizure-preventing effect of transmeningeal muscimol in rats. EEG seizure duration ratio = EEG seizure duration in minutes/acetylcholine exposure duration (9.5 minutes). ACSF, artificial cerebrospinal fluid. (b) The dual peristaltic minipump unit of the subdural HNP, with its cover removed to illustrate the inner structure.

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Development of the HNP software

The HNP software is designed to execute three functions: electrophysiological data acquisition, online seizure prediction/seizure recognition, and hardware control. A computationally inexpensive, vector analysis-based EEG seizure-recognition program was developed [9]. We found increased multineuron activity to be a predominant early sign of ictal events, preceding the onset of ACh- and kainic-acid-induced neocortical seizures in rats [10]. Presently we are exploring whether this phenomenon can be used to help with the seizure prediction module of the HNP software.

Challenges

The current challenges are to (1) test the safety of the integrated and fully implanted hardware in nonhuman primates, (2) complete the software of the device, (3) determine whether on-demand AED delivery yields better seizure prevention and fewer side effects than intermittent or continuous delivery, (4) build on this set of information and optimize the subdural drug delivery conditions in the clinical neurosurgical setting, and (5) identify the patient population for which subdural HNP implantation can significantly improve seizure control.

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3.5. Convection-enhanced delivery of anticonvulsant toxins for the treatment of intractable partial epilepsy

Michael A. Rogawski

A variety of approaches have been investigated for delivery of anticonvulsant substances directly into the central nervous system (CNS) to treat epilepsy [1]. These approaches provide the potential to use substances for epilepsy therapy, such as peptides, that are not orally active or blood–brain barrier permeable. Some direct delivery approaches involve targeted application into brain regions responsible for the initiation or spread of seizures. A major factor limiting the utility of systemic (e.g., oral or intravenous) drug administration is that the therapeutic agent is delivered to regions of the brain not responsible for seizure generation, with the possibility of side effects from actions on these bystander brain regions. Targeted delivery overcomes this limitation. Traditional CNS delivery methods such as intrathecal or intraventricular administration do not provide targeted delivery. Intraparenchymal bolus deposition (focal injection) is promising but does not allow control over the region of delivery, and the large concentration gradient obtained with this method does not provide for uniform delivery throughout an epileptic brain region [2]. With intraparenchymal bolus deposition, the active agent is distributed by diffusion so that this method is useful mainly for diffusible substances, which include traditional small-molecule AEDs. Moreover, as discussed below, such agents dissipate from the injection site rapidly. This requires continuous delivery to obtain sustained seizure protection. Alternatively, it has been proposed that the drug be injected when needed, such as when triggered by a seizure prediction or detection system, but this depends on reliable detection methods that markedly increase the technical complexity. The use of drug-eluting polymer wafers is of potential interest for high-potency, diffusible compounds but also does not allow the delivery volume to be controlled, and as with focal injection, the drug concentration profile is highly nonuniform. Finally, there has been significant interest in gene therapy approaches with vectors-expressing, for example, galanin or neuropeptide Y, or in the use of transplanted engineered cells or even stem cells [3–5]. All of these approaches have promise but there are substantial scientific and technical hurdles. An alternative approach to targeted direct CNS administration is convection-enhanced delivery (CED).

CED is a direct intraparenchymal drug delivery technique that uses a bulk flow mechanism to deliver and distribute a therapeutic agent homogeneously throughout clinically significant volumes of solid tissue [6–9]. This approach offers a greater volume of distribution than simple diffusion (e.g., with bolus deposition) and is designed to distribute a drug uniformly throughout a specific target region (Fig. 21). In this technique, the therapeutic agent is delivered by slow infusion of a solution into the interstitial space under positive pressure through a fine cannula. CED relies on bulk flow driven by hydrostatic pressure derived from a pump to carry the drug molecules within the extracellular spaces of the CNS. As CED does not depend on diffusion for distribution of the infused agent, it is not limited by the molecular weight, concentration, or diffusivity of the therapeutic agent. With CED, the blood–brain barrier is bypassed and specific regions in the CNS can be targeted, including regions defined as epileptic foci and identified for resection by a conventional presurgical evaluation.

Based on the properties of bulk flow, CED can be used to distribute both small and large molecules reliably, safely, and homogeneously over a range of volumes. Unlike intraparenchymal bolus deposition, CED does not cause structural or functional damage of the infused tissue and provides greater control over the distribution of the therapeutic substance. In CED, solutes are distributed homogeneously throughout a distribution volume that is proportional to the infusion volume regardless of the solute's molecular weight. CED is particularly applicable to slowly diffusing substances of high molecular weight, as the distribution of such large solutes is effectively restricted to the region of the infusion, providing greater control over the spatial extent of delivery than is obtained with bolus delivery. Currently available AEDs do not meet

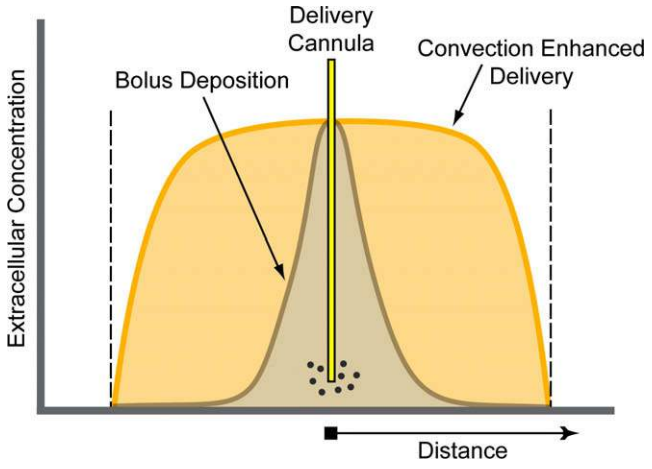

Fig. 21. Comparison of the extracellular fluid concentration for intraparenchymal bolus deposition (focal injection) and intraparenchymal convection enhanced delivery. The region perfused is delimited by the dashed lines. With bolus deposition, solute is distributed by diffusion, resulting in a rapidly declining concentration gradient throughout the region perfused. In contrast, convection enhanced delivery provides a uniform concentration throughout the region perfused with a sharp drop-off in concentration at the borders.

these criteria. However, several peptide toxins, including conotoxins and botulinum neurotoxins, have been studied and appear to be appropriate for CED [10]. The toxins that have been studied are potent inhibitors of neurotransmitter release. In in vitro and in vivo experimental epilepsy models, the toxins have been found to inhibit epileptiform discharges [11, 12]. The toxins have physiochemical properties that are favorable for CED. They are of appropriate molecular size, and are highly potent, highly polar/hydrophilic, and stable. Because of their properties, diffusion through brain tissue is limited. Therefore, when they are deposited by CED, they remain at the site of deposition for long periods, providing for prolonged antiseizure activity.

Studies on N-type calcium channel antagonists in the rat kindling model

Highly selective peptide N-type calcium channel antagonists, including ω-conotoxin GVIA and ω-conotoxin MVIIA, inhibit calcium influx into presynaptic nerve terminals and thereby potently suppress synaptic transmission. Because of the physiochemical properties noted above, the toxins are not orally active and they distribute poorly in brain by diffusion. They do, however, have anticonvulsant activity when administered at high doses intraventricularly, but with installation into the cerebrospinal fluid, seizure protection is accompanied by profound generalized tremor [13]. In the rat amygdala kindling model, we recently demonstrated that localized CED infusion of ?-conotoxin GVIA and ?-conotoxin MVIIA into the amygdala produces a long-lasting elevation in afterdischarge threshold [10]. The toxins also cause a dose-dependent reduction in seizure parameters, including afterdischarge duration and duration of behavioral limbic seizure activity. The protective effects of the toxins reached a maximum at 48 h postinfusion, and then gradually resolved over the next 5 days. In contrast, the AED carbamazepine was active at 20 min but not at 24 h after the infusion. Except for transient tremor in some rats receiving supratherapeutic toxin doses, no adverse effects were observed. In control experiments, inactivated (proteolyzed) ?-conotoxin MVIIA failed to affect seizure parameters.

It is noteworthy that although the infusion duration was only 20 minutes, seizure protection was obtained for nearly 1 week. The persistent action raises the possibility that local CED application of the toxins may be a practical approach to treat partial-onset seizures that fail to respond adequately to oral AEDs. The toxins could be administered intermittently via an indwelling infusion catheter system, with either an external or an implanted pump. The prolonged duration of action of the conotoxins is presumed to be due to their hydrophilicity, which causes them to remain in the extracellular space at the site of deposition. Carbamazepine and other AEDs, by contrast, are strongly hydrophobic molecules that readily diffuse across biological membranes and, therefore, can easily leave the site of deposition, thus accounting for their transient seizure protection.

Clinical application

Our results indicate that anticonvulsant toxins delivered locally using the CED technique can produce a long-lasting elevation in seizure threshold in an experimental epilepsy model. We therefore propose that CED could be used therapeutically to treat partial seizures in patients with defined seizure foci. Given the high success rate achieved with resective surgery in appropriately selected patients with intractable epilepsy [14], it is reasonable to hypothesize that silencing the brain region to be resected may offer efficacy similar to that of surgery while sparing the brain otherwise targeted for resection. In addition to its use in patients who are candidates for resective surgery, the approach may also be of value in patients who are not surgical candidates because (1) their focus is near an eloquent brain region, (2) the patient is not sufficiently medically stable to undergo major brain surgery, or (3) the patient wishes to avoid the risks of craniotomy and brain resection.

The specific ways in which CED would be used in practice remain to be defined. In recent years, substantial advances have been made in CED technologies, primarily from studies on the experimental treatment of brain tumors, which could be applied in epilepsy. Toxin solutions could be administered with one or more implanted delivery catheters. Ultrafine catheters (0.2-mm outside diameter at tip) are available in MRI-compatible materials (polyurethane and fused silica) that produce minimal tissue damage and can remain implanted for long periods. Antireflux designs prevent tracking of the infusion fluid up the catheter. Initial delivery of the toxin solution could be performed while the patient is being monitored with scalp or depth EEG. Incorporation of imaging tracers (such as gadolinium for MRI) would allow the distribution of the therapeutic agent to be monitored in real time during the infusion, providing an opportunity to adjust the delivery volume, and catheter placement to achieve targeting of the desired brain volume without leakage [15]. Patients would be reinfused through the implanted catheters at intervals. Reinfusion could be accelerated if breakthrough seizures occurred or by other EEG criteria. A major advantage of the CED approach over resective surgery is that it is reversible and could be discontinued if ineffective of if unacceptable side effects occurred. The approach may also be used as a diagnostic method to localize the seizure focus and to define the critical extent of tissue that requires removal.

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3.6. Distributed microstimulation for epilepsy

John D. Rolston, Steve M. Potter, Robert E. Gross

Electrical stimulation is a promising therapy for pharmacoresistant seizures [1–3], and is currently being tested in a variety of instantiations, such as deep brain stimulation (DBS) of subcortical nuclei, responsive stimulation of the cortex, and vagus nerve stimulation . Each of these approaches uses a small number (usually =4) of large, millimeter-diameter electrodes, and relatively high currents and frequencies (several mA, often at >100 Hz). Although many of these methods have shown evidence of reducing seizure frequency, they so far have achieved seizure freedom in only a small number of patients.

We have taken an alternative approach, using arrays of microelectrodes (dozens with diameters <50 μm) to directly stimulate epileptic foci with low-frequency, low-current pulses, asynchronously delivered across the span of the electrode array . This method was shown to be completely effective in suppressing epileptiform bursting in cultures of dissociated rat neocortex , a valuable model of the brain that reproduces some of its most nuanced features . Population bursting, which underlies interictal activity in vivo , was suppressed in all cultures tested. For effective stimulation, only 25 of the 59 available electrodes were used, with each electrode stimulated at 2 Hz (50 Hz aggregate for the entire array). Stimulation was voltage controlled and biphasic, using custom-made hardware , and ranged from 100 to 900 mV per 400-μs phase. Optimal stimulation parameters for evoking neural responses had been previously determined . Importantly, single-electrode stimulation, like that used in conventional DBS, was incapable of suppressing bursting, even at higher stimulation voltages .

In an attempt to further optimize this protocol, we developed a closed-loop, state-control algorithm to adjust stimulation parameters in real time . State control uses the output of a system (e.g., neural activity) to change the activity of a controller, which acts to move the sensed output closer to a desired value (also called the reference value). In this case, the controller was multielectrode distributed stimulation, with stimulation voltage as the controller's free parameter. For input to the control algorithm, we monitored the array-wide firing rate f (i.e., the number of action potentials recorded from all electrodes per second), which can be viewed as a state variable of the neuronal network. As higher-voltage stimulation leads to increased neural firing rates in vitro , we could control the firing rate by adjusting the voltage of ongoing stimulation, using the control equation

$$V_{new} \leftarrow V_{prev}\left(1 - \varepsilon \frac{f - f_0}{f_0}\right)$$

where V_{new} is the stimulation voltage, V_{prev} is the previously used stimulation voltage, f is the observed array-wide firing rate, f_0 is a target (reference) firing rate, andis a gain factor determining how quickly V reacts to f (typically, $å$ = 0.02).

This closed-loop approach again led to suppression of epileptiform activity, but did so with greater efficiency. Specifically, at a stimulation rate of 10 Hz aggregate with only 10 randomly selected electrodes (1 Hz per electrode), closed-loop stimulation suppressed epileptiform activity in >50% of cultures tested, compared with 20% with open-loop distributed stimulation at the same rate and electrode number. If electrodes were selected for efficacy in advance (rather than randomly), closed-loop stimulation was effective in 80% of cultures, compared with 60% of open-loop experiments in this reduced rate and reduced electrode number setup.

The primary advantages of the state-control approach are (1) reduced stimulation frequency and (2) a decreased need to find ef-

Fig. 22. Photograph of the RNS System neurostimulator and schematic of the neurostimulator sited in the cranium and connected to one depth lead and one subdural strip lead.

Please cite this article in press as: Schachter SC et al. Advances in the Application of Technology to Epilepsy: The CIMIT/NIO Epilepsy Innovation Summit Epilepsy Behav (2009), doi:10.1016/j.yebeh.2009.06.028

fective electrodes. These, in turn, lead to additional advantages beyond those already offered by open-loop distributed microstimulation: (1) reduced need for system programming postimplantation (a frequent problem in contemporary DBS treatments), (2) increased battery life (due to lower voltages and stimulation rates), and (3) the potential to automatically compensate for brain changes or electrode impedance changes; for example, if the brain adapts and requires larger stimulation voltages, or the electrode impedance increases yielding a similar effect, the algorithm will automatically provide increased stimulation voltages. Other advantages common to both open- and closed-loop stimulation include increased fault tolerance (with more electrodes, there is increased physical redundancy) and relaxed placement requirements (more electrodes increase the probability of electrically affecting critical neural tissue).

Why should distributed stimulation suppress epileptiform activity? Neuronal cultures by definition lack the afferent and efferent connections they had in vivo. For reasons that are still unclear, such isolation causes a numerical increase and strengthening of recurrent synapses among the remaining neurons, perhaps in a homeostatic attempt to substitute for lost input [12–14]. In vivo, this might best be approximated by deafferentation epilepsy, where part of the neocortex is undercut, removing afferent drive and producing spontaneous seizures after a period of cortical reorganization [15,16]. Furthermore, similar epileptiform activity occurs in the hippocampus when deafferention [12,17], and low-frequency "reafferentation" suppress this activity [18]. Distributed microstimulation may thus work by something akin to "reafferentation" of our cultures.

We are currently extending this work to behaving animals. We have developed a system for closed-loop stimulation and microwire array recording *in vivo* [19] and are in the process of validating our protocols. In general, the rapid advances in real-time capabilities of computers and embedded systems, in tandem with progress in multielectrode recording and stimulation in awake animals (including humans), promise an exciting time for closed-loop strategies for treating a wide array of neurological and psychiatric disorders [20–22].

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3.7. The NeuroPace RNS System

Martha J. Morrell

The NeuroPace RNS System is an investigational device that delivers responsive stimulation to the brain and is being evaluated as an adjunctive therapy for adults with medically intractable partial-onset seizures. The RNS System (Fig. 22) includes a cranially implanted, programmable, battery-powered, microprocessor-controlled neurostimulator that is connected to depth and/or subdural strip leads, a programmer for physicians to program settings and retrieve stored information from the neurostimulator, a patient data transmitter for remote monitoring, and a telemetry wand for wireless communication between the neurostimulator and the programmer or remote patient monitor.

Electrographic data storage is triggered by detection, responsive stimulation, scheduled time-of-day, magnet (used by the patient to indicate a clinical event), and/or other events as programmed by the physician. These data allow physicians to assess detection sensitivity and effects of stimulation.

Three detection tools are provided. The half-wave tool (similar to [1]) detects spikes and rhythmic activity occurring in specific frequency ranges. The line length algorithm [2] identifies changes in both amplitude and frequency. The area feature [3] identifies changes in overall signal energy without regard for frequency. The physician adjusts the detection tools for each patient.

The neurostimulator delivers current-controlled, charge-balanced biphasic pulses programmed by the physician to deliver stimulation frequencies ranging from 1 to 333 Hz, current ampli-

tudes from 1 to 12 mA, and pulse widths from 40 to 1000 ìs. The stimulation montage is configured to deliver current between any combination of electrodes and the neurostimulator case.

Up to five individually configured sequential therapies of electrical stimulation may be programmed, each composed of two independently configurable bursts. The neurostimulator will attempt to re-detect the epileptiform activity after each stimulation therapy is delivered. If the epileptiform activity is still detected, the next (sequential) therapy will be delivered. If the epileptiform activity is no longer detected, the remaining therapies will not be delivered and the episode ends.

Clinical trials

A 2-year, multicenter feasibility trial in 65 adult subjects aged 16 to 65 with medically intractable partial-onset seizures arising from one or two epileptogenic onset regions collected safety and preliminary efficacy data after implantation of the RNS System Neurostimulator and Leads, and was followed by a 5-year, long-term treatment trial.

Subjects with =12 simple partial (SP) sensory or motor seizures, complex partial seizures (CPSs), and/or generalized tonic–clonic seizures (GTCSs) over an 84-day baseline period qualified for the study. Safety was monitored continuously. Efficacy was assessed over the 84 days beginning 1 month postimplantation, over the most recent 84 days of participation, and over the subject's entire participation.

During the first 84-day efficacy assessment, the responder rate (percentage of subjects with a 50% reduction in seizures) in 50 subjects (excluding 1 subject with no disabling seizures at baseline and 14 subjects blinded off) was 27% (12/44) for CPS, 65% (11/17) for GTCSs, and 24% (12/50) for total disabling seizures (SP motor seizures, CPSs, and GTCSs).

For the most recent 84-day period (as of April 21, 2008), the responder rate for total disabling seizures in 60 subjects (excluding 1 subject with no disabling seizures at baseline and 4 subjects with incomplete or inconsistent seizure frequency data) was 48%. The responder rate for subjects with seizure onsets in the hippocampus was 74% (14/19) and that for seizure onsets in the neocortex was 37% (15/41). The responder rate for all subjects increased from 25% at 3 months of treatment ($n = 64$) to 48% at 18 months ($n = 61$).

A randomized, double-blind, multicenter, sham-controlled trial is currently underway to evaluate the safety and efficacy of the RNS System as adjunctive therapy for medically refractory partial-onset epilepsy. The investigation enrolled 240 adult subjects (18–70 years of age) who have an average of three or more disabling SP motor seizures, CPSs, and/or secondarily generalized seizures per 28 days. Subjects are followed for 2 years postimplantation and then can be followed for an additional 5 years within the Long-Term Treatment Trial.

Combining the experience from the Feasibility, Pivotal, and Long-Term Treatment trials, as of June 10, 2009, 256 subjects had been implanted with the RNS Neurostimulator and Leads for a total of 494 implant years and a total of 427 stimulation years with no unanticipated serious device-related adverse events.

Discussion

Responsive neurostimulation may be a safe and effective treatment option for adults with medically intractable partial-onset seizures [4, 5] and may offer advantages to current therapy options because it treats just the seizure focus only when needed, and is reversible if desired. A feasibility and long-term treatment investigation of the RNS System demonstrated safety and a sustained reduction in disabling seizures in 65 adults with intractable partial-onset epilepsy. However, completion of well-designed clinical trials currently in progress is necessary to further assess safety and to establish efficacy.

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3.8. Neurostimulation for epilepsy, including a pilot study of anterior nucleus stimulation

Nina M. Graves

Although electrical stimulation of the central nervous system for treatment of epilepsy is investigational, it may become a potential therapy for individuals with refractory epilepsy [1–3], because stimulation might be expected to work by mechanisms different from those invoked by medications or focal surgery.

The initial work on thalamic stimulation for epilepsy was performed by the New York neurosurgeon Irving Cooper. In 1980, Cooper, Upton, and Amin [4–7] initiated anterior nucleus (AN) stimulation and, over the next 4 years, implanted six patients, four of whom were said to have improved seizure control. Two of the patients also showed improvement in temporal hypometabolism assessed by PET scans [7]. Sussman and colleagues [8] employed the Cooper protocol in anterior thalamus stimulation in five patients with previously intractable seizures. In a study presented in abstract form, they reported improvement in three of the five.

Several brain sites have been the target of stimulation to treat seizures in patients, including cerebellum, caudate, brainstem, subthalamus, and thalamus. There are several review articles that discuss the history and current status of deep brain stimulation (DBS) for epilepsy [9–15].

The possible mechanism of action for DBS for epilepsy is unknown. Several mechanisms have been postulated for brain stimulation in the treatment of movement disorders. There are four general hypotheses: depolarization blockade, synaptic inhibition, synaptic depression, and stimulation-induced modulation of pathological network activity [16].

Rationale for AN stimulation

Animal work done after Cooper's clinical studies has tended to support the AN as a possible target for electrical stimulation. Mirski and Ferrendelli mapped metabolic activation in guinea pig brain during seizures induced by pentylenetetrazol [17]. Particularly active were posterior hypothalamus in the region of the mammillary bodies and the anterior thalamus via its connection by the mammillothalamic tract [18]. Lesions of the mammillothalamic tract increased the threshold for inducing seizures. Mirski and Fisher [19] used electrical stimulation of posterior hypothalamus as a functional method of inhibition. The threshold for pentylenetetrazol-induced clonic convulsions was doubled in the presence of such stimulation. Effects of stimulation could be imitated by injection

of the inhibitory GABA agonist muscimol. Because mammillary bodies were considered to be a difficult stereotactic target, attention was directed to the anterior nuclei of thalamus, which are strongly linked to posterior hypothalamus. Stimulation of the AN bilaterally in the rat inhibited cortical epileptiform EEG discharges after systemic administration of pentylenetetrazol [20]. High-frequency stimulation in the range of 100/s was effective, whereas low-frequency stimulation less than 10/s did not inhibit seizures when delivered either to posterior hypothalamus or to the AN of thalamus. Stimulation of the anterior thalamus also could inhibit seizures generated by the excitatory amino acid drug kainic acid, given by systemic injection. Hamani et al. [21] published work in a pilocarpine model of seizures in which the animals were subjected to unilateral or bilateral AN thalamotomies or unilateral or bilateral AN stimulation. Bilateral stimulation significantly prolonged the latency to status epilepticus development, whereas no animal with bilateral thalamotomies developed seizures after pilocarpine administration. Unilateral stimulation or lesions produced effects that were no different from those of controls. This work was expanded [22] to explore stimulation of the AN of the thalamus using various parameters. Latency to seizures was prolonged 1.9- to 2.2-fold with AN stimulation at 500 ìA. The effect was more pronounced with higher current delivery. Two stimulation frequencies were tested (20 and 130 Hz). These changes did not significantly impact the results. Pulse width was not varied between the tests.

Clinical experience with stimulation of the AN of the thalamus in patients with epilepsy

Pilot study

In 1998, a group of investigators began collaboration on the design of studies to explore the use of neurostimulation of the AN in patients with uncontrolled seizures. Investigators have presented their individual findings at American Epilepsy Society meetings and have individually published some of these data [23–25].

The study designs prescribed intermittent high-frequency electrical stimulation of the AN of the thalamus in patients with intractable epilepsy. Bilateral programmable electrical stimulation devices were implanted over the anterior chest wall, with bilateral stereotactic implantation of the multicontact stimulation wires into the AN of the thalamus. The patients (seven male, seven female, age range: 19–47) were from four clinical sites and, at the time of summary of the data, had been followed for at least 12 months. All patients had medically intractable epilepsy. Changes in seizure frequency were assessed relative to a preimplantation (baseline) seizure frequency. The results from all 14 patients are summarized in Table 2, and those from the subgroup of patients with seizure onset in the temporal or frontal lobes, in Table 3.

Pivotal study.

In 2003, a pivotal clinical study of AN thalamic stimulation was started. The study was conducted at 17 centers in the United States. In 2008, all 110 implanted patients completed at least 13 months of follow-up postimplantation. The results of the study were presented in December 2008 at the American Epilepsy Society annual meeting. The study's primary objective was met, and the results have been submitted for publication and for FDA review.

This study was a multicenter, prospective, randomized, double-blind, parallel design study to evaluate the safety and efficacy of bilateral neurostimulation of the AN of the thalamus using a fully implantable DBS system (Fig. 23) as adjunctive therapy in adults diagnosed with epilepsy characterized by partial-onset seizures, with or without secondary generalization. The study was divided into multiple phases, illustrated in Fig. 24.

The primary efficacy objective was to demonstrate that the reduction in the seizure rate was greater in the active group than in the control group at the end of the blinded phase.

Key inclusion criteria included:

- Partial-onset seizures with or without secondary generalization.
- Anticipated average of six or more partial-onset seizures (with or without secondary generalized seizures) per month during the baseline phase.
- Refractory to antiepileptic drugs (AEDs) [Patients were considered refractory if their seizures failed to significantly improve with at least three AEDs due to lack of efficacy].
- Age between 18 and 65 at the time of lead implant.

Key exclusion criteria included:

- IQ less than 70 based on the Baseline Week –12 WASI test.
- Symptomatic generalized epilepsy.

Conclusion

A randomized, double-blind, placebo-controlled, parallel-design study of AN thalamic stimulation has been completed in the United

Table 2
Percentage change in seizure frequency (compared with baseline) and responder rate in the 14 AN pilot patients.[a]

	Months 1–3		Months 4–6		Months 1–12	
	% Change	% Responders	% Change	% Responders	% Change	% Responders
Mean	−55.9	57.1	−41.1	57.1	−44.9	57.1
Median	−63.8		−63.3		−55.8	
SD	33.9		52.9		39.2	

[a] A responder is defined as an individual with a 50% or greater decrease in seizure frequency.

Table 3
Percentage change in seizure frequency (compared with baseline) and responder rate in the nine AN pilot patients with seizures presumed to originate in the temporal or frontal lobes.[a]

	Months 1–3		Months 4–6		Months 1–12	
	% Change	% Responders	% Change	% Responders	% Change	% Responders
Mean	−61.1	77.8	−41.1	66.7	−45.5	66.7
Median	−78.8		−64.6		−58.6	
SD	40.8		65.2		47.2	

[a] A responder is defined as an individual with a 50% or greater decrease in seizure frequency.

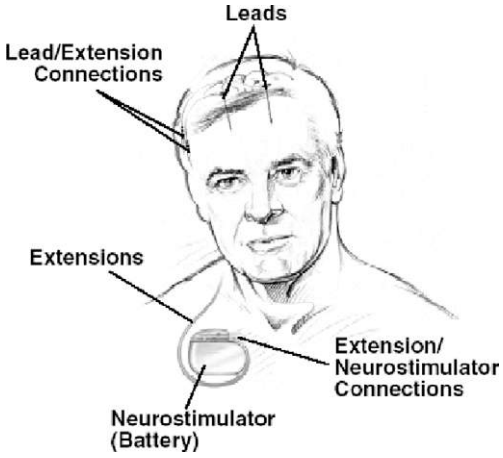

Fig. 23. Drawing showing bilateral leads, extensions and neurostimulator (Kinetra; Medtronic).

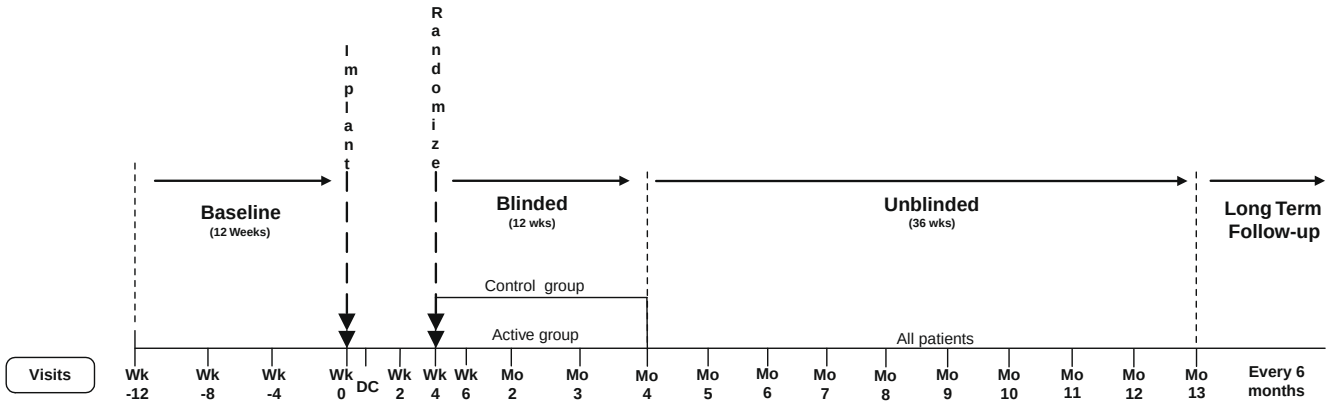

Fig. 24. SANTE study design.

States, and should serve to thoroughly assess the safety and efficacy of stimulation of this anatomic target for epilepsy.

3.9. A "topological" approach to seizure abatement: Oscillations' phases, direct current pulses, and the elusive "null space"

Ivan Osorio, Mark G. Frei

Biological oscillators, of which neurons are a special class, generate oscillations with characteristic frequencies and phases. These oscillations can be investigated from a topological perspective to identify regions ("null spaces" or "black holes") into which they can be "pushed" ("resetting" the oscillation's phase), using monophasic (direct current [DC]) pulses delivered at a "critical" phase/time during their cycle [1-3]. Cardiac standstill caused by closed chest trauma is an example of the fate of oscillations "pushed" into the "null space," a singularity that is "present" in neuronal and axonal preparations [1]. The investigation of the intracellular correlates of cortical afterdischarges (ADs) strongly suggests the existence of a "null space" for these oscillations [4, 5]; ADs consistently disappeared below and reappeared above a certain membrane potential; in other words, the ADs could be pushed into and outside a "null space." This observation becomes meaningful when put in the context of recent examples of blockage of ADs [6, 7] and seizures in humans [8] using electrical currents.

Cortical activity (ECoG or EEG) comprises voltage oscillations with phases that may be represented by rotating vectors, whose angular velocity w is related to the frequency f of the oscillations by $f = 1/T = w/2\eth$. More generally, the phase of an oscillation is the position in time of the oscillation with respect to a defined fiducial. Using phase relative to natural fiducial times such as those marking state transitions (into and out of seizures) and even points on waveforms of known relevance (e.g., the peak of a spike discharge) are rarely applied to the analysis of seizure time series of subjects with epilepsy.

The value of phase resetting for the study and control of arrhythmias has been exploited in the field of cardiology [9], but not in epileptology, despite its direct applicability and potential for shedding light on the mechanisms of seizure initiation and termination. This pilot study investigates the feasibility of seizure blockage (annihilation) using monophasic (DC) single or brief pulse trains.

Methods

Eight male Wistar rats weighing 300–450 g (Charles River Laboratories, Wilmington, MA, USA) were kept on 12-h light–dark cycles until the beginning of the experiment and had free access to food and water. Experiments were conducted in compliance with all applicable federal statutes and regulations related to animals and experiments involving animals. On the day of the experiment, rats were preanesthetized with isoflurane. A subcutaneous injection of 67.5 mg/kg ketamine:3.4 mg/kg xylazine:0.67 mg/kg acepromazine was then administered for full anesthesia. Supplemental doses of 100 mg/mL ketamine were given at a rate of 0.2 mL/h to maintain a stable plane of anesthesia. The anesthetized rat was placed on a stereotaxic instrument (Harvard Apparatus, Holliston, MA, USA) and then connected to a Homeothermic Blanket Control Unit (Harvard Apparatus) to maintain body temperature at 37.0 ± 0.3 °C. A midline incision was made on the scalp and the skull was exposed. Four sterile electrodes (1-mm-outer-diameter stainless-steel screws) were placed over the cortex for recording of electrical activity. Two of the four electrodes were placed over the right hemisphere 4.2 mm anterior and 5.8 mm posterior and -1.4 mm lateral with respect to bregma; of the remaining electrodes, one was used as a ground and the other as a reference (nasion).

Seizures were induced with a GABA inhibitor, 3-mercaptopropionic acid (3-MPA) 70 mg/kg, administered as an intravenous bolus. When 3-MPA brain concentration was maximal, the seizures were generalized tonic–clonic.

Data recording and analysis.

ECoG was recorded with Synamps II amplifiers (Neuroscan, Inc. El Paso, TX, USA). Recording settings were DC – 2 kHz (10 or 20 kHz, sampling rate, 24 bits of precision). On- and offline analyses for seizure detection and single waves (within a seizure burst) were performed visually and with a validated algorithm [10].

The degree of morphological similarity among waves (denoted herein as *rhythmicity index* [RI]) that make up seizures, an indirect measure of neuronal synchronization level, was measured using the autocorrelation function. Autocorrelation is a mathematical tool for finding repeating patterns and may be simply defined as the "cross-correlation" of a signal with itself. This function was written into a computer program for online automated quantification and triggering of monophasic electrical stimulation (ES). The rationale for this approach was born out of the observation that the probability of seizure annihilation by ES was much higher when the morphology of the waves forming a seizure was monomorphic or stereotypical than when the waves were relatively polymorphic (Fig. 25).

Electrical stimulation

ES was performed using a commercial stimulator (Grass S12; Quincy, MA, USA) that delivers approximately charge-balanced (biphasic) square pulses. This device was modified to deliver monophasic pulses whose quality was verified visually.

ES consisted of (1) single and (2) brief (0.1-s) pulse trains at 50 Hz. Pulse delivery was either manual or automated using a program developed by the investigators; in either case, pulses were aimed at the ascending or descending parts of the wave or to its peak (global maxima). ES varied from 1.0 to 8.0 V (electrode impe-

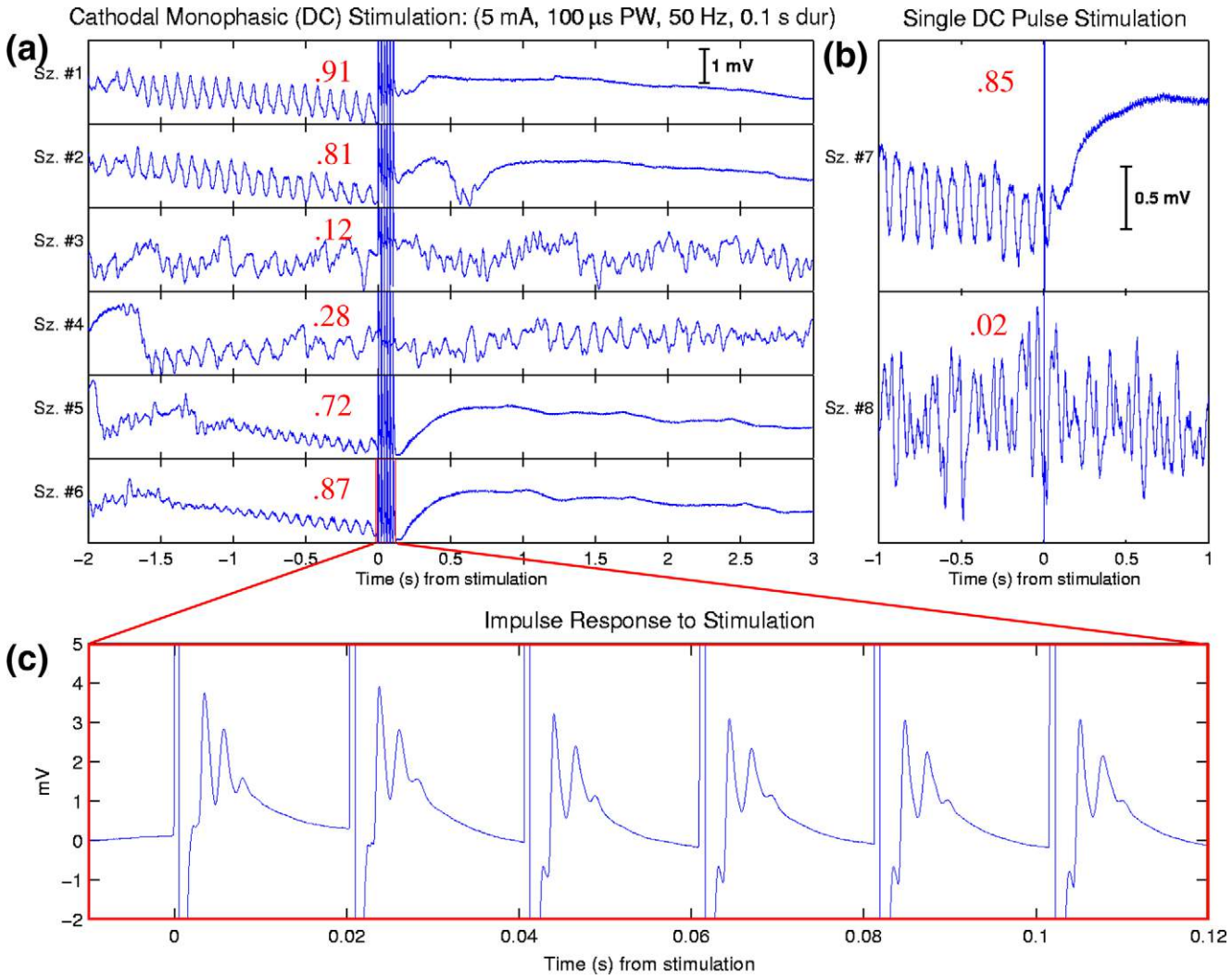

Fig. 25. Top left-hand panels depict six seizures recorded from one (representative) rat using subdural electrodes (activity from only one contact is shown) each treated with a total of six monophasic (cathodal) pulses delivered through the electrodes adjacent to those used for recording. Top right-hand panels depict two seizures treated with single monophasic (cathodal) pulses (5 mA, 100 ìs) also delivered adjacent to the recording electrodes (same rat). The numbers on top of each tracing to the left of the stimulation artifacts in each panel correspond to the "rhythmicity index," a measure of similarity between successive signal waveforms, computed using software developed by these investigators. Magnified view of six tissue impulse responses to each of the six monophasic pulses delivered over 0.12 s to seizure 6. The probability of seizure blockage is clearly a function of rhythmicity index value. The impulse responses to cathodal stimulations show subtle phase changes (resetting), possibly illustrative of their trajectory to the "null space" or "black hole" from where they cannot "escape" unless suitable stimuli are applied. Cardiac standstill and death (unless timely medical intervention occurs) caused by closed chest trauma exemplify the phenomenon of annihilation of biological oscillations and the existence of "black holes" in certain biological systems such as the heart. As an electrically oscillatory system, the brain likely also has "black hole(s)."

dances were ~1 kÙ), and pulse width was 100–200 ìs, but widths of up to 1 ms were occasionally used. Monophasic currents were delivered through two of four electrodes so as to span both hemispheres; the other two electrodes were used to record ECoG during stimulation.

Results

The mean number of stimulation trials per rat was 42, and more than one trial was often delivered to the same seizure. The rhythmicity index was nonstationary, varying during the course of seizures.

A total of 146 seizures received at least one DC pulse: Thirty (20%) of these seizures were annihilated by single pulse (No. 11) or brief pulse trains (0.1 s at 50 Hz, No. 19) and 29 of them contained at least one segment with rhythmicity indices >0.6 (Fig. 25). Only 1 of 30 seizures with a RI <0.6 that were stimulated was blocked by DC pulses. Single or brief monophasic pulse trains consistently failed to annihilate or reset to an appreciable degree the phase of seizure oscillations with a RI <0.6 (Fig. 25), regardless of the intensity, pulse width, and polarity of ES.

Discussion

All previous attempts known to the authors at phase resetting of neuronal oscillations have been limited to single cells, slice preparations, or computer models. Degree of phase synchronization as estimated using the autocorrelation function, and not neuronal mass or cytoarchitectonic considerations, appears to be the more critical factor in determining the probability of seizure annihilation. Seizures with a high degree of monomorphism (autocorrelation value >0.6) were consistently annihilated, possibly by being pushed into the "null space" by even single monophasic pulses (Fig. 25). Fully synchronized neuronal aggregates reach the vulnerable phase space simultaneously and are thus all susceptible to annihilation by well-timed single pulses, a hypothesis that may be tested in models of neuronal oscillations.

Unlike induced cardiac standstill, which if untreated is irreversible, seizures were only transiently suppressed, as this brain state

Please cite this article in press as: Schachter SC et al. Advances in the Application of Technology to Epilepsy: The CIMIT/NIO Epilepsy Innovation Summit Epilepsy Behav (2009), doi:10.1016/j.yebeh.2009.06.028

is inherently unstable and the convulsant remained at sufficiently high concentrations to sustain them. Recent successful attempts to transiently suppress oscillations of potentially epileptogenic neurons in the interictal state using single, brief cathodal DC pulses [11] may represent examples of phase resetting of large neuronal human aggregates. A less compelling, but plausible, example of phase resetting leading to transient annihilation of neuronal/axonal oscillations is the phenomenon known as *cathodal block* [12], described more than 100 years ago.

To date, all experimental and clinical demonstrations of phase resetting of biological oscillations have used direct or "monophasic" pulses (DC) [13, 14], which although theoretically more efficacious for seizure blockage than alternating or charge-balanced pulses, presumably have a greater cytotoxic potential. The greater efficiency of DC compared with AC charge-balanced pulses is likely due to the fact that although one of the phases of the AC pulse may "push" the oscillation into the "null space," the other phase, being of equal intensity but opposite polarity, "pulls" the oscillation back to near its original phase space. Charge-balanced (alternating current [AC]) pulses lack the "directionality" that DC pulses possess and that may be required to reset the phases of oscillations.

The main aim of this study was to investigate the feasibility of seizure blockage using single or brief monophasic (DC) pulse trains. Although it is speculated that phase resetting was the mechanism responsible for seizure blockage, proof of this was not offered. Inferences to be drawn from this work are: (1) the level of neuronal synchronization and timing of stimulation may be more important factors in determining the probability of seizure blockage than previously recognized, and (2) resetting of the phase of neuronal oscillations may be exploitable as an antiseizure therapy.

Acknowledgments. This research was supported by NIH Grant R21NS056022. N. Bhavaraju, Ph.D., C. Lunte, Ph.D., and E. Crick, Ph.D., provided valuable technical contributions.

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3.10. Focal cooling and uncaging: Possible therapeutic options for focal neocortical epilepsy

Steven M. Rothman

Although more than 80% of patients with temporal lobe epilepsy have excellent responses to surgical resection, the chance of seizure control after extratemporal resection is lower [1]. Moreover, some regions of the cortex subserving language, primary motor, and sensory functions are too vital for surgical resection. We have, therefore, started to explore nondestructive technologies that allow transient inactivation of epileptogenic neocortex.

The first technology is focal cooling with thermoelectric (Peltier) devices. These devices are composed of an array of semiconductors joining two thin ceramic wafers (Fig. 26A). The semiconductors are connected electrically in series but thermally in parallel, so that a current passing through the semiconductors cools one wafer and warms the other. The thickness of these devices can be less than 1 mm.

Several groups have used these devices to cool the cortical surface overlying an experimental epileptic focus and rapidly terminate seizures [2, 3]. It has also been possible to automatically activate cooling using a feedback circuit and seizure detection algorithm [4]. Further rodent experimentation documented that cooling as low as 5?C did not damage the cortex. We envision the eventual fabrication of an implantable cooling device in which the cold side of a Peltier chip is placed adjacent to the epileptic foci in the human neocortex. At seizure onset, the device would be activated to abort the seizure.

Several questions and problems have to be resolved before we can move ahead with commercialization:

1. How far does human cortical temperature need to be reduced to terminate a seizure? We know that rodent cortex requires cooling to 20 to 24?C to stop seizures, but that may be excessive for human seizures. The degree of temperature reduction will determine power consumption and heat dissipation for any commercial device, so it will be difficult to move ahead without this information. We are in the process of developing a fluid-based cooling device to try to obtain these data in humans during invasive mapping for epilepsy surgery.
2. How will heat be removed from the warm side of the Peltier device? We have preliminary data characterizing heat pipes that could contact the Peltier on one side and the dura or skull on the other [5].
3. What type of power supply will be used to generate the cooling? We suspect that conventional batteries may suffice, because the device duty cycle will only be a fraction of each day and cooling itself was effective for only a brief time interval (4–7 s).

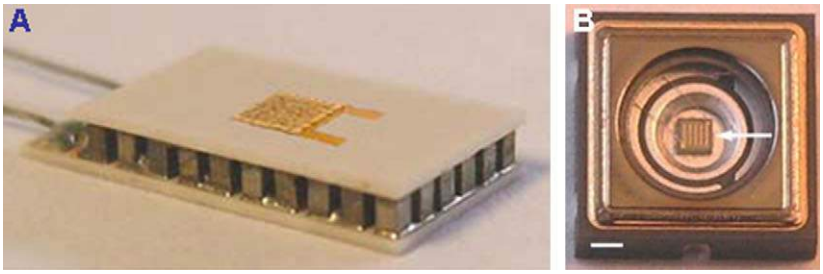

Fig. 26. (A) Photograph of two Peltier devices. On the bottom is a conventional device similar to those used in experimental epilepsy work to date. The smaller device on top was fabricated using new layering technology that is capable of generating ultrathin Peltier devices that are more efficient energetically. These latter devices would be more suitable for biomedical applications. (B) Photograph of a UV LED. The arrow points to the actual light-generating element. The scale in the lower right corner is 1 mm and applies to both (A) and (B).

A second technology under investigation is optical methodology to abort extratemporal-onset seizures. The spatial and temporal resolutions of optical methods are extremely appealing and several groups are already investigating optical control of neuronal activity [6]. Our approach has been to use a newly synthesized caged GABA, BC204, which releases GABA when illuminated at 360 nm [7]. We have employed an ultraviolet light-emitting diode (UV LED) for uncaging (Fig. 26B). This has the advantage of very small size (?1 mm) and low power requirements. In tissue culture, this light source can uncage BC204, eliciting GABAergic currents in individual neurons [8]. We also get adequate penetration from the UV LED to uncage BC204 in slices of rat brain to abort ictal-like activity. Ultimately we envision placing an array of UV LEDs above the epileptogenic cortex and applying caged compound in the subarachnoid space. A closed loop would activate the LED at seizure detection.

There are several important problems we need to overcome before this idea can be realized:

1. Is BC204 or a related caged GABA stable at body temperature and pH to remain active? At this point, we know that the compound is stable in culture and slice, but have no data on long-term in vivo stability.
2. Will BC204 diffuse from the subarachnoid space into cortex at high enough concentration to affect paroxysmal activity? Although the in vitro effects we have observed have been very impressive, the compound needs to penetrate into intact brain to be an effective antiepileptic drug.
3. Will ultraviolet light penetrate sufficiently far into intact brain to allow uncaging? We will have to show that there is sufficient light penetration in the long UV range to uncage BC204. Although our slice results suggest penetration to 500 ?m, there is concern that UV does not go as far as longer wavelengths.
4. Will either our caged compounds or the UV LED damage underlying brain? These wavelengths are typically benign, but will have to be tested under realistic conditions to identify possible neurotoxicity.

Acknowledgments. This work was partially funded by the Alafi Family Foundation and the NIH (R01 NS42936).

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4. Extracranial treatment systems

4.1. Overview

Steven C. Schachter

In parallel with the development of intracranial treatment systems, a growing number of extracranial approaches to the treatment of epilepsy are available commercially (vagus nerve stimulation) or are currently under evaluation in laboratory animals or patients with epilepsy. Noninvasive systems have the advantage of avoiding intracranial procedures as well as reversibility, but whether the relative imprecision in targeting therapy compared with intracranial devices lessens their effectiveness will await comparative studies. For those systems that incorporate seizure detection and prediction, further progress will occur together with advancements in algorithms, as described in Section 2, and wearable, wireless sensors of brain function or body movements.

4.2. Preliminary data on anticonvulsant efficacy of transcutaneous electrical stimulation via novel concentric ring electrodes

Walter Besio, Kanthaiah Koka, Karen Gale, Andrei Medvedev

The goal of this research was to establish the feasibility of controlling seizures in rat models with noninvasive transcutaneous electrical stimulation (TcES) via concentric ring electrodes. All animal protocols were approved by the Louisiana Tech University IACUC, 5/07. For all seizure models, male Sprague–Dawley rats (220–350 g) were used with three electrodes attached to their scalp. One electrode, used to record and stimulate, was centered on the top of the head. The other two recording electrodes were placed laterally behind the eyes, but in front of the ears (A 2.0 mm, L 9.0 mm rela-

tive to the central electrode) on both sides of the head. We discovered positive efficacy using TcES on three different rat seizure models: penicillin, pilocarpine (PILO), and pentylenetetrazol (PTZ).

Penicillin seizure model (intracisternal)

A small amount (approximately 0.2 cc) of cerebrospinal fluid was removed and replaced with penicillin G (2.5 MU/kg) [1]. Within 1 min, on average, myoclonic jerks began. Once the myoclonic jerks reached the rate of 30/min, TcES was applied to the central electrode. In the control group (n = 8), not receiving TcES, the average maximal myoclonic jerk rate was 70/min with an average duration of 90 minutes. In the experimental group (n = 17), various pulse widths and frequencies were examined. There was a significant decrease in the mean myoclonic jerk rate from 41/minute to 21/minute (P < 0.0001, two-sample t test) on the first application of TcES. After TcES, myoclonic jerks stopped in all instances for a few minutes and then returned with a smaller amplitude and a lower frequency. In 13 cases, repeated stimulation led to complete cessation of myoclonic jerks.

PILO seizure model

Approximately 24 h before the induction of seizures, the rats were briefly anesthetized, and tripolar concentric ring electrodes were attached to the shaved scalp [2]. On the following day, scopolamine methyl nitrate (2 mg/kg, ip) was administered to prevent peripheral cholinergic effects such as respiratory distress and dehydration, followed by PILO (310 mg/kg, ip) administration 30 minutes later.

Seizure activity was considered to have reached status epilepticus (SE) when there was continuous electrographic activity for at least 30 s during the waxing and waning stage [3]. Rats were randomly assigned to either a control group (n = 8) or an experimental group (n = 8). Symmetric, biphasic, charge-balanced, constant-current TcES pulses were applied to the experimental group only. Five minutes after the onset of SE, TcES was delivered via the outer ring and disk (with the middle ring floating) of the central electrode on the top of the head. The baseline electrographic activity of the experimental group was similar to that of the control group. SE onset started 19 to 40 minutes (27 ± 8) after the administration of PILO, which was not statistically different from that of the control group (P = 0.198, two-sample t test). Immediately after the application of TcES, attenuation of electrographic seizure activity was evident in all eight treated rats. In some cases, the EEG still resembled the baseline activity even 2 h after the administration of TcES, while the PILO was still active.

The behavioral activity of the control group progressed to Racine scores significantly higher than those of the experimental group (mean R = 5.88 vs R = 4.75, where R = 6, wild running fit was the maximum possible score; P = 0.0014, Mann–Whitney U test). The behavioral manifestations of the treated rats indicate that TcES halted the progression of the seizures. Twenty-four hours after the injection of PILO, six (75%) of the treated rats versus one (12.5%) of the controls were alive. A log-rank test for homogeneity was performed on Kaplan–Meier survival curves. There was a significant difference between the survival times of the controls and those of the TcES-treated rats (P = 0.046). These findings suggest that TcES administered 5 minutes after SE onset had a significant effect on PILO-induced SE electrographic and behavioral activity, and that the effect appeared to be long-lasting.

PTZ seizure model

The rats were briefly anesthetized and three concentric ring electrodes were attached to the shaved scalp. Approximately 24 h later, PTZ (45 mg/kg, ip) was administered, EEG was recorded, and TcES (50 mA, 300 Hz, 200 ìS for 2 minutes) was applied to the central electrode after the first myoclonic jerk. Control rats (n = 21) were prepared with the same procedure except that no current was passed through the electrode.

In the control group, electrographic changes preceded behavioral manifestations of seizure activity. The former appeared as clear high-frequency bursts of short duration, which continued up to 1 h after the behavioral manifestations of seizure activity had ceased. For the experimental group (n = 14), the electrographic activity increased after the administration of PTZ and then reverted toward baseline activity after the application of TcES. The power spectrum of the EEG spikes clearly showed a decrease in electrographic activity post-TcES.

All control animals progressed through various seizure stages, reaching Racine's scores of 5 (R = 5, rearing) or 6 (severe clonic activity with rearing and falling). Periods of myoclonic jerking appeared multiple times over the course of approximately 20 minutes. For the experimental group, after TcES, no behavioral seizure activity was evident in six rats and only a few myoclonic jerks were observed in the other eight rats. Thus, TcES interrupted PTZ-induced seizures, and the electrographic and behavioral activity reverted toward baseline.

In summary, the results from the three seizure models tested (induced by penicillin, PILO, and PTZ) suggest that TcES has anticonvulsant effects. Further rigorous testing is necessary for better control of confounding factors such as multiple stimulation parameters applied to the same rat and/or variation in the delivery of the convulsant, to determine the most efficient TcES parameters.

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4.3. Noninvasive brain stimulation for the treatment of epilepsy

Felipe Fregni

Documented therapeutic application of electric current in neurological disease dates back to as early as the first century A.D. during which Romans used an electric current generated by torpedo fish to treat a number of physical ailments, most notably headaches and other body pain [1]. Yet, despite the long history of electrical stimulation to treat different ailments, the investigation of electrical stimulation for epilepsy treatment is still in its infancy.

Several approaches using electrical stimulation for seizure control that target structures in the central or peripheral nervous system have been studied. To date, the vagus nerve stimulator is the only FDA-approved treatment for epilepsy that uses electrical stimulation. Other strategies under investigation use invasive brain stimulation, and target epileptogenic cortex or deep brain structures, such as thalamic nuclei, as described in Section 3. However, invasive brain stimulation is a costly procedure associated with surgical risks. One alternative option is the use of noninvasive brain stimulation. Here we discuss two techniques of noninvasive brain stimulation: transcranial magnetic stimulation and transcranial direct current stimulation.

In the mid-1980s, Barker and colleagues introduced a novel technique of noninvasive brain stimulation—transcranial magnetic stimulation (TMS) [2]. TMS is based on the principle of electromag-

netic induction in which small focal intracranial electrical currents are generated by a powerful fluctuating extracranial electric field. Single pulses of current can be of sufficient magnitude to depolarize neurons transiently, but when these currents are applied in prolonged trains of stimuli, an approach known as repetitive TMS (rTMS), they can modulate cortical excitability, decreasing it with low-frequency stimulation (=1 Hz) and increasing it with high-frequency stimulation (=10 Hz). Notably, this change in excitability outlasts the duration of the rTMS train [3].

Another method of noninvasive brain stimulation is transcranial direct current stimulation (tDCS), which delivers weak polarizing direct currents to the cortex via two electrodes placed on the scalp: an active electrode placed on the site overlying the cortical target, and a reference electrode usually placed over the contralateral supraorbital area or in a noncephalic region. tDCS acts by inducing sustained changes in neural cell membrane potential: cathodal tDCS leads to brain hyperpolarization (inhibition), whereas anodal tDCS results in brain depolarization (excitation) [4, 5]. In patients with epilepsy, targeting seizure foci with inhibitory (?1 Hz) rTMS or inhibitory cathodal tDCS may be predicted to suppress activity of the epileptic focus through the induction of long-term depression-like effects [6, 7]. Currently, however, there are only a limited number of studies that have looked at the effects of either rTMS or tDCS for the treatment of epilepsy.

Three randomized, sham-controlled studies of rTMS in focal epilepsy have been published. Theodore et al. [8] performed the first randomized, controlled trial and found that active 1-Hz rTMS applied to the epileptic focus (as measured using EEG) does not significantly alter the number of seizures in subjects with epilepsy as compared with a sham control group, although there was a trend toward improvement ($P = 0.06$). It should be noted that this study recruited subjects whose epileptogenic zones were not of neocortical origin, but were rather located in deeper structures, such as the mesial temporal area. Indeed patients with neocortical foci had a greater reduction in seizure frequency as compared with those with mesial temporal foci [8].

Based on the hypothesis that patients with cortical foci might have a greater clinical response to low-frequency rTMS, Fregni et al. [9] performed a subsequent randomized, sham-controlled trial using parameters similar to those of the Theodore et al. study, but recruited subjects whose epileptic foci were of neocortical origin. Using 1-Hz stimulation for 20 minutes daily over a 5-day period, the investigators found a significant decrease in the number of seizures between the active rTMS group and those receiving sham treatment. This effect was apparent for days following the treatment, as well as more than 2 months after treatment, thus showing a long-lasting modulatory effect [9]. Additionally, the rTMS effect was also evident on the EEG, which showed a reduction in epileptiform discharges (EDs) in the active group when compared with baseline. As with the clinical response, the ED reduction was apparent immediately after 5-day rTMS treatment (reduction of 31%, $P = 0.0012$) and was still present at week 4 (reduction of 16%, $P = 0.027$). However, the EEG improvement tended to wash out at the week 8 follow-up (reduction of 14%, $P = 0.09$). In the sham rTMS group, the number of EDs compared with baseline did not change immediately after treatment ($P = 0.63$) or at week 4 ($P = 0.48$) or 8 ($P = 0.69$).

Finally, a third recent multicenter study did not show that rTMS is associated with a significant antiepileptic effect. Forty-three patients with drug-resistant epilepsy from eight centers underwent a randomized, double-blind, sham-controlled, crossover study assessing the clinical and EEG effects of low-frequency, 0.3-Hz rTMS. One thousand stimuli per day were given at 100% of motor threshold intensity for 5 consecutive days, with a round coil at the vertex. Results showed no significant reduction in seizures after 0.3-Hz rTMS compared with placebo. However, investigators found decreased interictal EEG abnormalities in one-third of the patients [10].

In the only study to evaluate the effects of tDCS on seizures and epileptiform discharges, Fregni et al. [11] used cathodal DC stimulation to induce a decrease in cortical excitability in patients with cortical dysplasia and found a reduction in the number of epileptiform discharges (EDs) in the EEG. Patients who received active DC polarization had a decrease in the mean number of EDs from 413.9 ± 427.1 (baseline) to 148.0 ± 168.2 (after stimulation), whereas patients who received sham DC polarization had a nonsignificant, small decrease in EDs from 334.4 ± 619.5 to 315.0 ± 632.5. Seizure frequency was also measured and compared between baseline and the period after DC polarization. None of the patients in the active treatment group reported an increase in seizure frequency after the treatment, and there was a trend for seizure reduction. This study suggested that active cathodal DC polarization in patients with a single focus was significantly effective in reducing EDs compared with the similar group of patients that received sham treatment.

In conclusion, although some invasive forms of brain stimulation are more established as alternative treatments for epilepsy, the initial results of noninvasive brain stimulation studies, although mixed, are encouraging. Importantly, optimal stimulation parameters and patient selection still need to be determined. Future studies combining TMS with neuroimaging techniques might help to identify cortical areas with dysfunctional activity and to thereby better focus the induced electric field. An interesting observation in need of further investigation is that in some patients, the antiepileptic effect of rTMS continues long after the end of the treatment, suggesting that durable plastic changes in synaptic strength can be induced by rTMS. At the very least, noninvasive brain stimulation might provide a valuable screening and guidance tool for the implantation of epidural or subdural electrodes for cortical stimulation.

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Please cite this article in press as: Schachter SC et al. Advances in the Application of Technology to Epilepsy: The CIMIT/NIO Epilepsy Innovation Summit Epilepsy Behav (2009), doi:10.1016/j.yebeh.2009.06.028

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4.4. Transcranial magnetic stimulation and transcranial direct current stimulation: Role of animal studies

Alexander Rotenberg

Two methods for noninvasive focal brain stimulation—repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS)—are emerging as novel tools in the management of clinical epilepsy.

rTMS is a technique based on the principle of electromagnetic induction, where small focal intracranial currents are generated by a powerful fluctuating extracranial magnetic field. The currents generated by rTMS are sufficient to induce action potentials in a small volume of cortex . By stimulating at a low (=1 Hz) rate, rTMS holds promise as a method to induce a lasting reduction in cortical excitability, which appears in a time course similar to that of long-term depression (LTD) in association with low-frequency electrical stimulation . In clinical applications, low-frequency rTMS delivered over a seizure focus may reduce seizure frequency in patients with epilepsy or interrupt instances of epilepsia partialis continua (EPC) . However, results to date in controlled trials have been mixed, with some controlled trials showing only modest therapeutic efficacy .

tDCS is a method for cortical stimulation with prolonged (=10 minute) low-amplitude ($\leq$2 mA) electrical current that is delivered through scalp electrodes . With this technique, the magnitude of the current is insufficient to trigger action potentials in a volume of cortical tissue. Rather, its application in clinical epilepsy is based on observations that neuronal activity is reduced in the region closer to the cathodal current source, and that this reduction outlasts the stimulation in a manner that also resembles LTD. As with TMS, clinical experience with cathodal tDCS in epilepsy is limited. One trial demonstrated reduced frequency of epileptiform discharges on EEG, but no change in clinical seizure frequency .

The clinical results of rTMS and cathodal tDCS to date suggest that translational research is warranted, such as in rat seizure models, which offer the capacity to test a range of stimulation paradigms in a relatively homogenous subject population. Further, translational work enables investigation of mechanisms that is otherwise difficult in human subjects. Specifically, experiments with rTMS and tDCS can enable investigations as to how closely the changes induced by these methods resemble those of classic in vitro LTD.

We recently developed methods for high-quality EEG combined with rTMS in seizing rats to evaluate whether rTMS can reliably attenuate ongoing seizures, and to test whether its anticonvulsive effect is dependent on stimulus frequency in the rat intraperitoneal kainate (KA) seizure model. We also tested whether EEG-guided "closed-loop" responsive rTMS that is administered when a seizure is detected on the EEG is practical and effective in suppressing ictal discharges. Our data show an encouraging potential to identify and treat ongoing seizures with rTMS and an anticonvulsive effect in the higher end (0.5–Hz) of the low-frequency rTMS spectrum. The contribution of LTD-like molecular changes to the rTMS antiepileptic potential is currently under investigation in our laboratory.

We have also taken advantage of rat seizure models to test the anticonvulsive potential of tDCS. In the pentylenetetrazol (PTZ) rat model as well as in the neonatal hypoxic rat seizure model, we have found a reduction in immediate early gene expression with tDCS, perhaps reflecting an anticonvulsive effect. As with rTMS, the contributions of LTD-like synaptic changes are currently under investigation.

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4.5. Vagus nerve stimulation: Neural network modulation

Reese Terry, Jr.

Vagus nerve stimulation (VNS) was approved in July 1997 for adults and adolescents over 12 years of age with partial-onset seizures that are refractory to antiepileptic medications. In the clinical trials, the median percentage seizure reduction was 34% at 3 months and 45% at 12 months [1]. Since its approval, more than 50,000 patients have been treated with VNS, and many authors have noted improvement in effectiveness with increased clinical experience; Amar and Apuzzo [2] reported a responder rate of 62.5% and Spanaki and colleagues [3] reported a 72% mean seizure reduction. In addition, an increased understanding of the neural networks affected by VNS is reflected in several recent reports. Cunningham and colleagues [4] described acute bilateral activation of c-Fos in the nucleus of the solitary tract (NTS) and activation after 3 weeks of c-Fos and ÄFosB in the locus coeruleus (LC). Dorr and Debonnel [5] described increased firing rates in the dorsal raphe nucleus over 90 days. This progress with clinical application and understanding of mechanism of action has stimulated questions and ideas for advancing VNS strategies and technology.

Patients seem to respond about the same across seizure types, age, and location of seizure onset (data on file with Cyberonics),

Please cite this article in press as: Schachter SC et al. Advances in the Application of Technology to Epilepsy: The CIMIT/NIO Epilepsy Innovation Summit Epilepsy Behav (2009), doi:10.1016/j.yebeh.2009.06.028

and data mining continues in the search for predictors of response. Response to external stimulation might be investigated as a surrogate for VNS, specifically transcranial direct current stimulation [6] and trigeminal nerve stimulation [7].

VNS activation through a wearable, closed-loop seizure detection system has been proposed [8] as the next step in VNS technology. Woodbury and Woodbury [9] reported that seizure duration was associated with the interval between seizure onset and initiation of VNS in rats, and Morris [10] reported greater improvement from on-demand stimulation among patients with active magnets versus those with sham magnets. The most logical approach for seizure detection would be EEG detection through surface, cortical, or deep brain electrodes. Shoeb and colleagues [11] reported success with surface EEG detection, and Sun and colleagues [12] reported success with cortical EEG seizure detection. Developing robust detection algorithms is challenging, but designing implantable electrodes that continue to function reliably over tens of years is even more challenging. A somewhat simpler approach, detecting a sudden change in the heart rate as an early indicator of seizures, has been proposed. Increased heart rate has been reported in 87% of seizures, and the increase preceded EEG seizure onset by an average of 8–14 s, depending on seizure type [13]. Applying randomly, rather than regularly delivered (chronic) stimulation during seizures has been suggested as a method for reversing epileptogenesis and was found to influence the epileptogenesis process in monkeys when VNS was activated through a closed-loop seizure detection system [14].

In clinical use, stimulation parameters have been limited to frequencies of 1 to 30 Hz and ON times from 7 s to 1 min. Many patients have benefited clinically with this restricted set of therapeutic options, but the possibility that use of novel VNS parameter settings or different patterns of stimulation could improve the effectiveness of VNS for more patients should be explored. Establishing more effective parameter-setting strategies comprises three components: (1) defining the combination of parameters that optimally stimulate the vagus nerve; (2) identifying the factors that enhance signal transmission through the nucleus tractus solitarius (NTS); and (3) determining how the target brain structures process the signals.

The maximum programmable frequency commercially available is 30 Hz. In comparison, investigations of deep brain stimulation (DBS) and external trigeminal nerve stimulation all use frequencies in the range of 145 Hz. Some evidence suggests that higher frequencies have equal, if not greater, effectiveness [15]. Higher frequencies may be particularly effective when delivered during a seizure [14]. However, higher frequencies delivered periodically may be less comfortable for the patient and reduce battery life. Ito and Craig [16] noted that delivering a few pulses at a high frequency every few seconds facilitates synaptic transfer and optimizes the measured evoked potentials in the parafasicular nucleus of primates and that the parafascicular nucleus may be involved in the antiepileptic effects of VNS.

With the goal of optimizing stimulation parameters for clinical effectivness, attention has been directed to several aspects of stimulation delivery: random delivery, increased duration, and bilateral stimulation. Random stimulation has been suggested as a means to avoid accommodation during periodic stimulation [14]. With respect to increasing the duration of stimulation, most patients are treated with a 30-s ON time or less, but the E01 clinical study used a 60-s ON time [15], and Takaya and colleagues [17] indicated that a 60-minute ON time was more effective than the standard 30-s ON/5-min OFF in rats. For patients whose seizures occur during certain times of the day or month, a circadian method of increased and decreased stimulation may be useful, thereby potentially improving effectiveness [4].

The success of bilateral deep brain stimulation for the control of Parkinson's disease suggests that bilateral stimulation of the vagus nerve may improve effectiveness. Although unilateral stimulation produces bilateral effects in the brain [4], the effect of bilateral stimulation might be additive and improve effectiveness. Another advantage of synchronized bilateral stimulation is the possibility of alternating stimulation patterns between the right and left vagus nerves.

In summary, a number of strategies hold promise for improving VNS effectiveness and should be investigated in the future.

Conflict of interest statement

The author is the founder, board member, and a stockholder of Cyberonics, Inc., manufacturer of the VNS system. Richard Rudolph, M.D., consultant to and stockholder of Cyberonics, performed medical review. Susan E. Siefert, ELS, CBC, principal, medical writing, and Cyberonics stockholder provided editorial assistance.

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Please cite this article in press as: Schachter SC et al. Advances in the Application of Technology to Epilepsy: The CIMIT/NIO Epilepsy Innovation Summit Epilepsy Behav (2009), doi:10.1016/j.yebeh.2009.06.028

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4.6. A patient-specific algorithm for detecting seizure onset and its use in closed-loop systems

Ali Hossam Schoeb, Trudy Pang, John Guttag, Steven C. Schachter

Patients with medically refractory epilepsy may be candidates for non-pharmacological therapies such as vagus nerve stimulation (VNS). VNS is delivered in two modes. In automatic mode, the implanted pulse generator automatically delivers stimulation to the vagus nerve at programmed intervals. In on-demand mode, the patient or her or his caregiver initiates vagus nerve stimulation in response to symptoms of a seizure by holding a permanent magnet for 1–2 s over the implanted pulse generator.

A number of clinical investigations have suggested that on-demand mode VNS, especially on electrographic seizure onset, can acutely affect the progression of a seizure. Hammond et al. [1] recorded a scalp EEG tracing illustrating the abrupt termination of an electrographic and behavioral seizure following the initiation of on-demand VNS. Morris [2] retrospectively analyzed seizure diaries from the E04 trial [3] and noted that 53% of patients capable of receiving on-demand stimulation reported seizure termination or diminution.

Unfortunately, a significant proportion of patients implanted with VNS are unable to initiate on-demand stimulation and instead must depend on others to do so [4], which has two consequences: (1) patients are denied the potential therapeutic benefit of on-demand stimulation when seizures occur in the absence of caregivers, and (2) there may be inconsistency in the outcomes when caregivers are present because they may not be able to initiate on-demand stimulation immediately on the clinical onset of a seizure. A computerized system that automatically initiates on-demand mode VNS rapidly on computerized detection of the electrographic onset of a seizure is therefore desirable.

We have designed and are clinically evaluating a computerized system that automatically initiates on-demand VNS following computerized detection of the onset of electrographic seizure activity from noninvasive scalp and ECG electrodes. The computerized system is composed of a commercial acquisition system (Digitrace 1800 Plus from SleepMed Inc) that collects the scalp EEG (SEEG) and ECG of a patient; a computer that receives and analyzes both the SEEG and ECG in real time using patient-specific algorithms [5]; and an electromagnet that is worn by the patient and positioned so that it rests over the implanted VNS pulse generator.

When the computerized system detects the onset of a seizure through analysis of the SEEG or ECG signal streams, it energizes the electromagnet worn by the patient. The magnetic field produced by the electromagnet triggers the implanted generator to initiate on-demand VNS via the same mechanism that is engaged when a permanent magnet is held briefly over the implanted generator.

Pilot clinical studies have evaluated the sensitivity and specificity of the algorithm and the time lag from onset of electrographic seizures to detection and to initiation of VNS. As an example, during an 81-h study of one patient, the computerized system detected five of five electrographic seizures and initiated on-demand VNS within 5 s of the appearance of ictal discharges in the scalp EEG (Fig. 27). During the same testing session, the computerized system initiated false stimulations at the rate of one false stimulation every 2.5 h. Ongoing studies are evaluating the clinical impact of computerized initiation of on-demand VNS on seizure progression.

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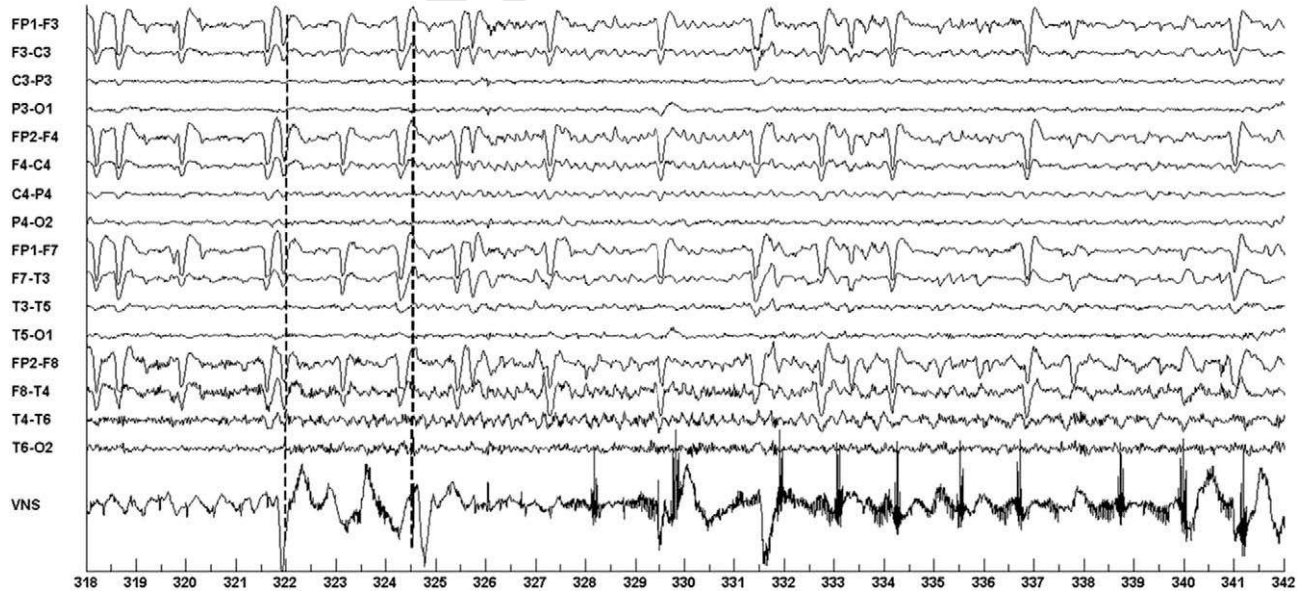

Fig. 27. EEG tracing of a spontaneous seizure (begins following the 322-s mark) with 3- to 4-Hz rhythmic activity seen on channels T4–T6, F4–C4, and C4–P4. The algorithm detected the seizure at the 324.5-s mark after which the electromagnet was energized, thereby initiating on-demand VNS following the 328-s mark (appears as a spike train on the VNS channel). The 6-s delay between seizure onset and the appearance of the VNS spike train is the sum of the following latencies: 2.5-s detection delay, 1.5- electromagnet on-time delay, and 2-s VNS startup time delay.

Please cite this article in press as: Schachter SC et al. Advances in the Application of Technology to Epilepsy: The CIMIT/NIO Epilepsy Innovation Summit Epilepsy Behav (2009), doi:10.1016/j.yebeh.2009.06.028

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4.7. Detecting seizures using wearable sensors

Shyamal Patel, Chiara Mancinelli, Ben Patritti, Trudy Pang, Steven Schachter, Paolo Bonato

Because seizures often cause loss of consciousness, it is difficult for individuals to objectively self-report the occurrence of seizures. However, seizure frequency is the primary criterion on which physicians make treatment decisions [1], and seizures do not respond to initial or replacement therapy in one of three patients with epilepsy. That is, the effectiveness of a given pharmacological treatment is based on evaluating its impact on the frequency of seizure events over an extended period. In practice, this assessment is performed by the patient or caregiver's quantifying seizure frequency, yet both measures are often inaccurate and misleading. The only objective way that is currently available to monitor seizures is to use specialized EEG monitoring equipment, which requires the use of scalp electrodes. Consequently, such monitoring is generally feasible only for periods than 1 week and, therefore, is used only to confirm the diagnosis of epilepsy, not to objectively quantify seizure frequency over extended periods. Hence there is a need for a noninvasive device that can chronically measure seizure frequency with high sensitivity and specificity.

Advances in miniature sensor technology and the development of small and powerful recording devices (e.g. PDAs) have fostered a significant interest in field-monitoring techniques [2–4] that can be used to study seizure events. Ambulatory systems to record EEG data in patients with epilepsy have been developed and used with some success. However, the attachment of electrodes on the scalp makes these systems quite obtrusive and impractical for long-term use. Further, not all epileptic seizures that give rise to stereotyped motor behavior can be detected from scalp electrodes, the best example being seizures of mesial frontal lobe origin.

Stereotypic seizure-related movements may vary from individual to individual but are generally consistent from seizure to seizure within any individual patient with epilepsy. Quantitative video analysis of movement patterns of adult patients with epilepsy during seizures has previously been undertaken using image-processing techniques [5]. More recently, the suitability of wearable sensors (accelerometers), positioned on the trunk and the four limbs, to detect seizure events in patients exhibiting different types of seizures (myoclonic, clonic, and tonic seizures) has been evaluated by Nijsen et al. [6], who reported positive results in 18 patients with epilepsy. However, two major limitations of their study need to be addressed. First, accelerometer data were analyzed only by visual inspection. Long-term, continuous monitoring of seizure events will likely require the analysis of vast amounts of data that cannot be practically achieved via visual inspection of the recordings. Second, the likelihood of false detections of seizure events when individuals perform activities of daily living was not assessed. A very small likelihood of false-positive detections is an essential characteristic of our proposed signal processing algorithms.

Ongoing work by our team relies on wearable sensors to collect data from accelerometer and electromyographic probes over extended periods, thereby allowing us to assess the likelihood of false detection of seizure events when subjects perform activities of daily living. This evaluation is carried out on the basis of algorithms that we developed to automatically analyze the recordings from wearable movement and surface electromyographic (EMG) sensors with the aim of identifying patterns of motion and muscle activation that are associated with movements that accompany seizures. This short report provides an example of the results achieved in our ongoing study. We summarize the procedures implemented in one of the patients we recruited so far and the outcomes of the data analysis we obtained using an algorithm that we developed based on a decision tree approach.

Data were collected during a period of clinical observation of several days performed at Beth Israel Medical Deaconess Center in Boston from a patient undergoing seizure monitoring. Recordings were performed over2 days following gradual decrease in the dosage of AEDs. This individual experienced seizures that were accompanied by movements of one arm involving shoulder, elbow, and wrist flexion. Therefore, wireless, wearable units equipped with accelerometers were strapped to the affected upper arm and forearm to capture movements associated with seizures. Units equipped with electrodes to capture EMG data from wrist flexors and extensors were positioned on the forearm on the flexor digitorum and extensor digitorum muscles.

Data collected over 2 days included multiple seizure events as well as the performance of activities of daily living. Accelerometer data were processed to separate low-frequency components associated with gross postural changes and high-frequency components associated with movements of the limbs. EMG data were elaborated to derive the envelope of EMG activity via rectification and low-pass filtering of the raw data. Subsequently, the derived time series were segmented with a 10-s rectangular window, and features were computed including the root mean square value of the time series, its dominant frequency, and the approximate entropy. Then the C4.5 algorithm was used to build a decision tree that used a selected subset of features to detect the seizure onset based on the features derived from the accelerometer and EMG data. Clinical observations were used to generate training and testing sets, thus allowing us to achieve a preliminary assessment of the potential of wearable sensor technology for the detection of clinical seizure activity.

Our results in this single case study showed the ability of the proposed approach to provide correct classifications in approximately 98% of the analyzed data segments. This result is very encouraging as it indicates that wearable sensors could potentially be used to detect seizures that are accompanied by movements in patients with epilepsy.

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Please cite this article in press as: Schachter SC et al. Advances in the Application of Technology to Epilepsy: The CIMIT/NIO Epilepsy Innovation Summit Epilepsy Behav (2009), doi:10.1016/j.yebeh.2009.06.028

General acknowledgments. We gratefully acknowledge the enthusiastic support of the Epilepsy Therapy Project; John Parrish, DeAnna Grosbaum, and Beverly Brown of CIMIT, and Zack Lynch and the Neurotechnology Industry Organization.

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Please cite this article in press as: Schachter SC et al. Advances in the Application of Technology to Epilepsy: The CIMIT/NIO Epilepsy Innovation Summit Epilepsy Behav (2009), doi:10.1016/j.yebeh.2009.06.028