Novel Surgical Therapies for Epilepsy

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BACKGROUND

Despite advances in antiepileptic drug (AED) development, only 50 to 70% of epileptic patients are controlled with pharmacotherapy. With a point prevalence of 0.5 to 1.0% of the United States population afflicted with epilepsy, there are estimated to be hundreds of thousands of epileptics who are not seizure free on medical therapy. At least one-third of these patients are likely candidates for epilepsy surgery.[4] However, as shown in *Figure 17.1*, there is great variability in the percentage of patients rendered seizure free for different surgical pathologies and procedures. A clinical need exists for novel epilepsy treatments. *Table 17.1* outlines novel surgical therapies for epilepsy that are under investigation now or may be available in the near future. Complete discussion of all of these is beyond the scope of this presentation. The therapies marked with an asterisk will be highlighted.

NOVEL APPLICATION OF AN EXISTING SURGICAL APPROACH

There are several clinical examples in which existing neurosurgical techniques are being applied to epilepsy surgery in novel ways. These include: 1) early surgery for mesial temporal lobe epilepsy (MTLE); 2) endoscopic resection of hypothalamic hamartomas (HH); 3) gamma knife radiosurgery for MTLE or HH; and 4) bilateral deep brain stimulation.

Early Surgery for MTLE

There are many cogent arguments in favor of early surgical treatment in epilepsy. These include, but are not limited to:

- Seizures likely slow development and cause irreversible effects on the brain
- AEDs have adverse cognitive and behavioral side effects
- Psychosocial consequences may be alleviated or lessened if the patient becomes seizure-free

Mesial temporal lobe epilepsy is among the most common and most studied adult epilepsy surgeries. This epilepsy subtype is clearly definable based on interictal and ictal electroencephalography (EEG), temporal lobe magnetic resonance imaging (MRI), clinical semiology, and neuropsychological testing. Properly selected MTLE patients have excellent surgical results, with seizure free rates of 65% to more than 95% in selected clinical trials and institutional series.[25] However, despite the surgical success in treating MTLE, there is commonly a long delay from the time of diagnosis to surgical treatment in these patients. Whether or not early surgical treatment will result in better outcomes in terms of seizure freedom, neuropsychological testing, and psychosocial function is being tested in the ERSET trial. Being run by Jerome Engel at UCLA as the Principal Investigator (with Itzhak Fried as the neurosurgical PI), this study is a randomized controlled trial of medication refractory MTLE patients within 2 years of diagnosis who are being randomized to early surgery versus best medical therapy. Due to difficulties such as appropriately identifying MTLE patients and rapidly completing AED trials to demonstrate medication refractoriness, the enrollment in this study is lagging behind schedule.

Endoscopic Resection of Hypothalamic Hamartomas

Hypothalamic hamartomas are tumor-like masses of the hypothalamus made up of disorganized neuronal and glial elements. Previously poorly detected in the pre-MRI era, these lesions are now recognized to result in localization related epilepsy in a minority of (predominantly pediatric) epilepsy patients. HH epilepsy patients often have coexistent memory and behavioral dysfunction. Seizures in HH patients are typically poorly localized by scalp EEG and poorly responsive to antiepileptic therapy.

There are several classifications of HH based on MRI location, attachment plane with the hypothalamus, and size. All of these share the finding that it is the intrahypothalamic portion of the lesion that is thought to generate epilepsy in these patients. A number of open surgical options evolved over time for the management of these lesions, including pterional, orbitozygomatic, and subfrontal craniotomy approaches. However, the relatively high morbidity of these approaches directed the Melbourne group, led by Professor Rosenfeld, to modify the transcallosal interforniceal approach to the third ventricle to treat these anterior third ventricular lesions from above. As the goal of HH surgery is to disconnect the hamartoma from its lateral third ventricular wall

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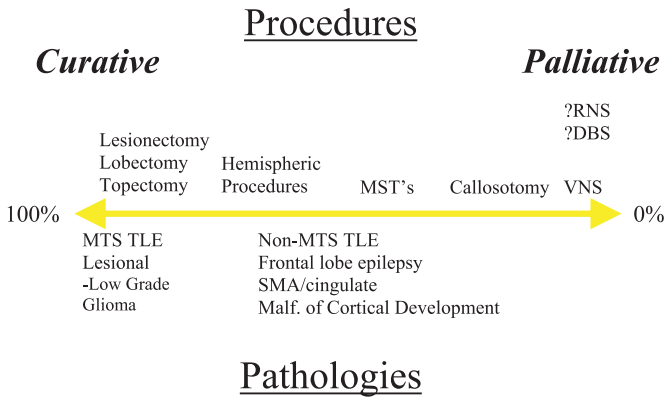

FIGURE 17.1 Epilepsy surgery: where we stand.

TABLE 17.1. Novel therapies for epilepsy

I. NOW
A. Novel Application of an Existing Technique
1. Early surgery (TLE)*
2. Endoscopy (Hypo. Hamartoma)*
3. Gamma Knife Radiosurgery*
4. Deep Brain Stimulation*
B. Technically Novel/Novel Concept
1. Feedback Stimulation*
II. IN THE FUTURE
A. Novel Application of an Existing Technique
1. Convection Enhanced Delivery*
B. Technically Novel
2. Predictive Devices*
3. fMRI/TMS based therapy
C. Novel Concept
1. Focal Cooling*
2. Gene Therapy

*Discussed further in this chapter

hypothalamic attachment, this approach is direct and efficacious. However, the approach has significant long-term potential morbidity, with 8 to 15% memory impairment, 4% diabetes insipidus, and 20% hyperphagia with weight gain.[5,8,15,18]

A more recent approach to HH surgery has been to use a transforaminal endoscopic approach from the contralateral side of the HH attachment to directly disconnect these lesions (*Fig. 17.2*).[3] While not technically feasible for some larger HH lesions, this approach is well suited for many of the small HH lesions that are found to cause epilepsy. Although not yet documented in large published series, the endoscopic approach, when it can be applied, may have lower surgical morbidity and equal efficacy as the open transcallosal approach.

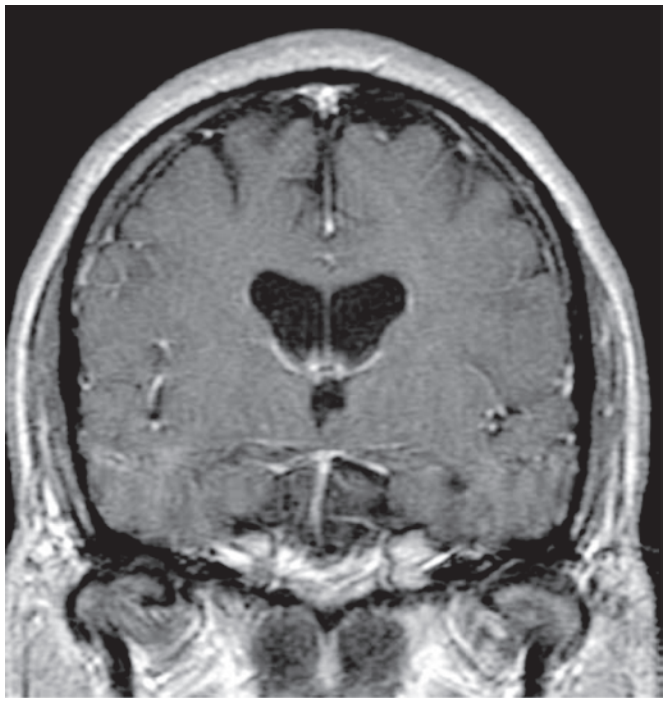

FIGURE 17.2 A contralateral endoscopic approach is well suited for small HH lesions.

Gamma Knife Radiosurgery for MTLE or HH

There is significant experience in the tumor and vascular (arteriovenous and cavernous malformation) neurosurgical subfields of focal radiation ameliorating or curing seizures. More recently, radiosurgery has been applied as primary treatment of epilepsy for MTLE and HH. The European experience in both of these arenas has been led by Professor Jean Regis in Marseilles.[21,22]

Radiosurgery is particularly appealing as a treatment for HH for smaller sessile lesions within the hypothalamus, a safe distance away from the optic tracts. The largest series of treated patients out of Marseilles includes 60 patients since 1999, 27 of whom had more than 3 years of follow-up.[23] Of these 27 patients, 59% (16 out of 27) are seizure free or have only rare gelastic seizures, whereas five are improved and retreatment is planned. Morbidity in this series was minimal, with three cases of transient poikilothermia. These numbers compare to slightly greater than 50% seizure freedom, with 76 to 89% of patients more than 90% improved, in the Barrow and Melbourne open transcallosal surgical series. The radiosurgical and open transcallosal series do not strictly compare "apples to apples" based on lesion size and plane of hypothalamic attachment. Recognizing this caveat, the available experience suggests that open surgical or endoscopic disconnection of an HH provides somewhat better seizure control, but at the cost of possibly higher morbidity than a radiosurgical treatment approach. Whether surgical discon-

nection or radiosurgery is better suited in an individual case of HH will be based on lesion location and size; patient/family preference; and surgeon experience, bias, and skill. Although these lesions are relatively rare, a randomized trial of open versus radiosurgical approaches for the treatment of HH related epilepsy is certainly justified.

Radiosurgery is also being studied in both Europe and the United States as an alternative to open surgical resection for TLE. In the United States, the treatment phase of a multicenter trial of radiosurgery for MTLE has been completed, and data on efficacy is being accumulated. The hypothesis of this trial was that radiosurgical treatment of patients with medically refractory temporal lobe epilepsy will result in significant reduction in seizures with minimal morbidity. Led by Professor Nicholas Barbaro at UCSF, this trial enrolled 30 patients across the United States, with randomization to 24 versus 20 Gray of treatment delivered to the temporal amygdala and anterior 2 cm of the hippocampus. The final outcome measure will be seizure freedom at 3 years, with secondary neuropsychological outcomes. Both the United States trial and a previous European multicenter trial of 20 patients are achieving at least 65% seizure freedom, at latest reporting. The permanence of efficacy, delayed complications, and long-term neuropsychological sequela remain to be determined. Based on available data, radiosurgery is a promising, but still experimental, therapy for TLE. The next phase of the United States trial, randomization of MTLE patients to open surgical versus radiosurgical treatment, is being planned.[1]

It is important to note that seizure control in any form of epilepsy treated with stereotactic radiosurgery is delayed, often more than 1 and up to 2 years after treatment. Many patients have transient increases in simple partial or other mild seizure phenotypes before to subsequent improvement.

Bilateral Deep Brain Stimulation (DBS)

Among several potential targets based on animal model data, the subthalamic nucleus (STN) and the anterior nucleus of the thalamus (AN) have been tried as target sites of bilateral DBS to treat epilepsy (*Fig. 17.3*). The AN is currently the focus of a multicenter Medtronic-sponsored, National Institutes of Health (NIH)-approved trial for the treatment of epilepsy. The logic of this trial is based in part on the following findings:

- AN stimulation can disrupt the limbic (Papez) circuit
- AN directly links to mesial frontal and temporal cortex
- Stimulation of the AN increases seizure threshold in phenylenetetrazol (PTZ) induced seizures in rats[16]
- Pilot studies of bilateral AN DBS in 14 patients showed an 8 out of 14 (57%) responder rate; 78% of patients responded in frontal/temporal lobe subset.[10,11]

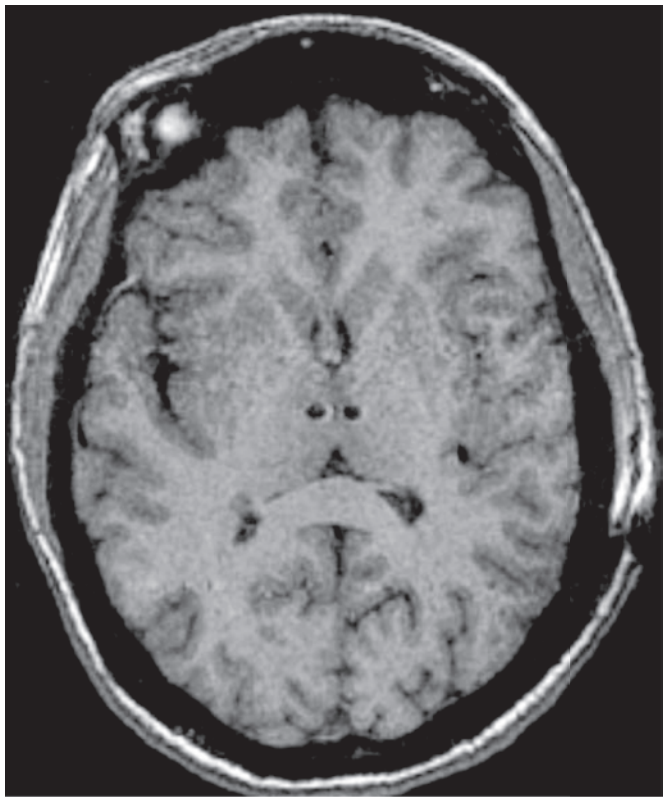

FIGURE 17.3 Bilateral AN thalamus DBS electrodes in place in an epilepsy patient.

The resulting trial, termed the SANTÉ trial ([Bilateral] *S*timulation of the *A*nterior *N*ucleus of the *T*halamus for *E*pilepsy), is currently enrolling patients. They must be medically intractable patients with localization related epilepsy. Their epilepsy can be multifocal, involving up to three lobes maximum. The study is designed for 124 patients to be enrolled at 12 sites, 124 patients. Based on the halfway point of enrollment, there have been no major complications. For the electrode targeting to the bilateral AN, microelectrode recording is at the discretion of individual site. No side effects have been observed with stimulation of the AN, even at maximum device levels. The results of this trial are eagerly anticipated.

NOVEL CONCEPT AND TECHNICAL: SEIZURE DETECTION AND RESPONSIVE THERAPY

A novel concept and technical approach in the treatment is the use of seizure detection software to identify an individual patient's seizure. This technology can then be paired with potential responsive therapies such as focal stimulation, convection enhanced drug delivery, or focal cooling (*Fig. 17.4*). In order to terminate clinical seizures by one of these treatment modalities, the seizure must be detected and

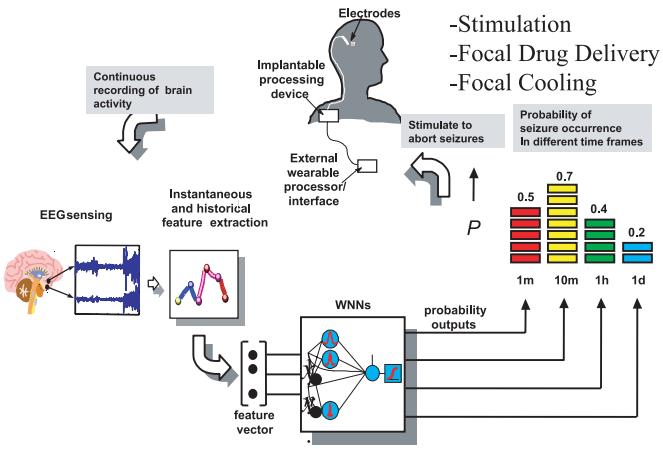

FIGURE 17.4 An implantable device to predict and treat seizures (courtesy Brian Litt, University of Pennsylvania).

treated before it spreads to a degree that it cannot be controlled with focal therapy. This suggests that these therapies will be most effective if treatment is delivered as early and precisely in the epileptic discharge as is possible, usually before the onset of clinical symptoms. Responsive stimulation thus requires sufficiently accurate seizure prediction algorithms (SPAs) for EEG recorded from intracranial electrodes.

All recent SPAs use a "sliding window analysis" in which a window of recorded EEG activity is mathematically analyzed using either linear or nonlinear algorithms. Linear algorithms calculate particular features directly from the EEG, including autocorrelation, spectral band analysis, curve length, accumulated energy, and high frequency epileptiform oscillations[14,17] nonlinear algorithms, the EEG sliding window is reconstructed in three-dimensional phase space and analyzed using techniques such as the short-term maximum Lyapunov exponent, dynamic similarity, or correlation dimension.[14,17] All of these techniques have been purported to have their advantages in seizure prediction. However, as discussed at the recent (Second Annual) Seizure Prediction Workshop in April 2006,[13] there is still much work to be done in terms of understanding and applying the basics of seizure dynamics. Future techniques will likely apply multi-channel, multi-algorithm integrated analysis, using a continuous probability curve rather than binary thresholding. In addition, the relevance of high frequency epileptiform oscillations prior to seizure onset will need to be determined and incorporated into future SPAs. It is likely that future seizure prediction and detection in an individual patient will use more than one SPA, and that the optimal SPA application profile will differ from patient to patient.

RESPONSIVE NEUROSTIMULATION

Once a seizure has been detected or predicted, a focal therapy must be applied to stop the ictal progression. While responsive stimulation, drug delivery, and focal cooling are all potential therapies, only responsive stimulation has reached device production and human clinical trial. Responsive stimulation, as currently available, differs from deep brain stimulation in two major ways: 1) Deep brain stimulation involves continuous open-loop therapy delivered into a target region of interest. It is delivered all the time without detection of brain activity in the target or feedback from the target tissue. In contrast, responsive stimulation is closed-loop. It is delivered intermittently in response to detected EEG abnormalities; 2) The pulse generator for available DBS systems is implanted in the chest wall below the clavicle, while the currently available responsive stimulator in implanted entirely within the skull.

The field of responsive stimulation already has examples of effective clinical application in human epilepsy patients. Osorio et al.[19] at the University of Kansas applied high frequency electrical stimulation that was delivered either directly to the epileptogenic zone (local closed-loop, n = 4 patients) or to the bilateral anterior thalamic nuclei (remote closed-loop, n = 4 patients) in response to every other automated seizure detection. The eight patients had a baseline video-EEG monitoring with implanted subdural and depth electrodes that localized epileptic foci and quantified seizure frequency using a linear SGA. Patients determined to have multifocal onsets were implanted into the bilateral thalami for remote stimulation, whereas local therapy was delivered to patients with a precisely localized epileptogenic focus. The mean reduction in seizure rate in the local closed-loop group was 55%; in the three responders the mean decrease was 86%, with two patients rendered seizure free during the local stimulation therapy. In the remote thalamic closed-loop stimulation, the mean seizure reduction rate was 41%, with a 74% reduction in the two responders.

More recently, patients undergoing subdural and depth electrode monitoring for seizure localization and functional mapping were enrolled in a trial testing an externalized version of an implantable responsive neurostimulator (eRNS, NeuroPace, Inc., Mountain View, CA).[12] This device used linear SPAs that could be tuned to patient-specific epileptiform activity to deliver electrical stimulation through up to eight contacts of a combination of subdural and/or depth electrodes implanted at the epileptogenic zone. Of 50 enrolled patients, 40 received responsive stimulation. The experience with four of these patients was subsequently reported. In this trial, electrographic seizures were altered and suppressed in these patients during trials of neurostimulation, with no major side effects. In one patient, stimulation appeared also to improve the baseline EEG.

Implantation of an internalized version of this responsive neurostimulator (RNS) system was subsequently investigated in a multicenter clinical trial assessing feasibility of the device's clinical implantation and implementation (*Fig.*

17.5). For this trial, enrollment included subjects 18 to 65 years with intractable partial-onset seizures and localized epileptogenic onset region(s). Subjects with at least 12 simple partial (SP) sensory or motor seizures, complex partial seizures (CPS) or generalized tonic-clonic (GTC) seizures over an 84-day baseline period qualified for implant. The responsive stimulator was connected to up to two four-contact leads (subdural and/or depth), which were targeted to the seizure focus. This trial's results have been reported in limited fashion. A single center's experience with eight implants resulted in 45% reduction in seizure frequency in seven out of eight patients over more than 9 months of follow-up.[6] For the multicenter trial, efficacy was assessed during the most recent 84 days for which a subject could have received therapy. Defining response as greater than or equal to 50% reduction in seizures, the responder rate for 56 subjects was 36% for CPS, 50% for GTC, and 36% for totally disabling seizures (TDS). The median percentage reduction was: CPS 28%, GTC 50% and TDS 30%; seizure reduction was significant for CPS ($P < 0.005$), GTC ($P < 0.02$), and TDS ($P < 0.001$). In 65 implanted subjects, including 17 device replacements, there were no serious unanticipated device-related adverse events. Responsive neurostimulation was well tolerated by the patients.[7] In follow-up to the feasibility trial, a clinical efficacy trial is beginning enrollment in the Fall of 2006.

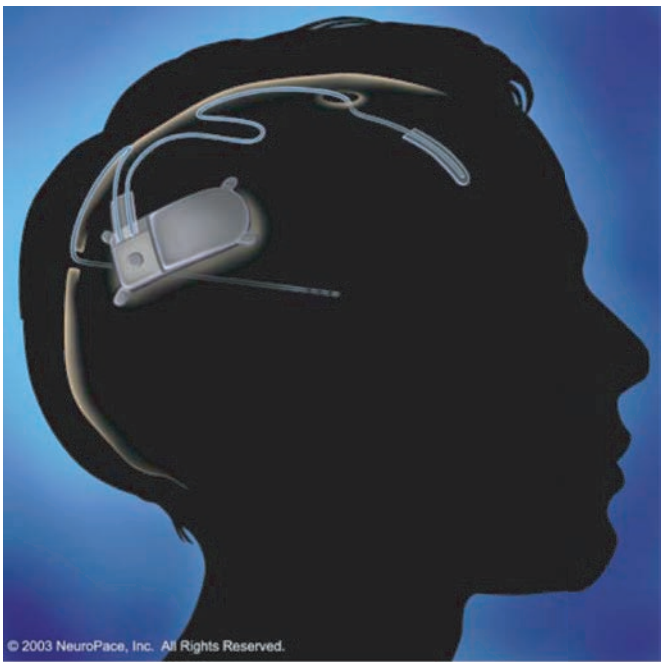

FIGURE 17.5 Schematic diagram of the implantable responsive stimulation device currently in human trial (Courtesy NeuroPace, Inc.)

Convection-enhanced Drug Delivery

An exciting, but untested, concept is the pairing of SPA technology to focal drug delivery. This would allow application of antiepileptic medication to the epileptogenic zone only in response to an impending seizure. Convection enhanced delivery (CED) of pharmocotherapeutic agents is already in trial in human malignant brain tumors, and has been experimentally applied in movement disorders and epilepsy. Drug is slowly infused into the brain through a small implanted catheter, using a low pressure pump, to maximize the volume of distribution and dose reliability.

In contrast to diffusion, which relies on a concentration gradient and is molecular weight dependent, CED involves bulk flow along a pressure gradient that is independent of the molecular weight of the applied drug. CED allows delivery of relatively homogeneous concentrations of drug along a larger volume of distribution than achieved by diffusion. By directly applying drug into brain tissue, it also bypasses the blood brain barrier, thus avoiding systemic toxicity. For the purposes of treating epilepsy, CED has potential applications in drug delivery paired with seizure prediction; in the reversible assessment of brain function, and as a method of focal neuromodulation.[9,20,24] In a primate model, the Surgical Neurology Branch at NIH has demonstrated targeted modulation of neuronal activity in the temporal lobe using muscimol (a GABA-A agonist) delivered by CED (*Fig. 17.6*).[9,20]

There are many obstacles to the successful development of CED therapy for epilepsy. These include being able to deliver drug rapidly following seizure detection or prediction, to prevent seizure spread beyond the focal region of detection. In addition, which targets are optimal and what drugs will work best as antiepileptic compounds when directly delivered into brain tissue remain to be determined.

Focal Cooling Therapy

Another exciting potential future surgical treatment of focal epilepsy is the application of focal cooling to stop seizures. In theory, this technology can also be paired with SPA technology. There is a building literature supporting the efficacy of

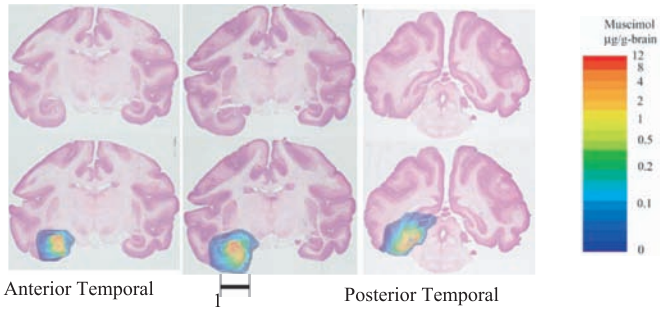

FIGURE 17.6 Muscimol autoradiography shows focal modulation of temporal lobe function with CED (Courtesy Surgical Neurology Branch, NINDS, NIH).

cooling as a treatment of epilepsy. Work in the Rothman lab at Washington University in St. Louis has shown that cooling provides effective in vitro and in vivo suppression of epileptiform activity in animal models. While the mechanisms of focal cooling's efficacy in terminating seizures are not clearly known, it has been shown to block presynaptic neurotransmitter release and can result in reversible dendritic spine changes.[2,26–28]

There is limited "brain cooling" efficacy data in refractory human epilepsy, largely due to ineffective technology to rapidly cool the brain. However, cold irrigation is effective in terminating stimulation induced and spontaneous epileptiform activity during awake craniotomies. Of particular interest, there is some evidence that cooling may selectively impact epileptiform activity while preserving normal brain function.

One approach to cooling the brain focally to treat epilepsy is to develop a Peltier device. A prototype Peltier device (that cools the applied surface by removing heat that is transferred to the opposite surface) has been instrumented for this purpose. Transient focal cooling to 5°C has been shown to be well tolerated by mammalian neocortex. Further work is necessary to see if: 1) a geometrically feasible design that can be applied to the brain's gyral structure can be developed; 2) focal cooling can be used to stop focal neocortical seizures in a primate model of epilepsy; and 3) intermittent focal brain cooling is well tolerated long term.

CONCLUSION

There are many promising novel surgical treatments of epilepsy. Existing technologies are being applied and new technologies are being developed. There is a need for noninvasive technology such as functional MRI based detection of interictal and ictal activity to provide a means of identifying focal epileptogenic zones. Identifying the focal seizure onset region is critical to guide the surgical placement of new technologies such as responsive stimulation or focal drug delivery or cooling. It is a very exciting time in epilepsy surgery, a field that will certainly look much different 10 years from now.

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