

Brain Stimulation for Epilepsy

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Ignited by the efficacy and commercial success of cardiac devices, neurologists, neurosurgeons, and biomedical engineers are collaborating to develop implantable brain devices to arrest, contain, and preempt seizures before they cause clinical symptoms. New devices in development deliver electrical stimulation or pharmacologic agents locally to the epileptic focus or deep nuclei to modulate seizure activity. “Blind” devices deliver therapy periodically, independent of ictal activity, while intelligent “closed-loop” systems trigger stimulation or drug infusion after interpreting electrical and/or chemical activity in the brain. Partnerships with industry are driving rapid translation of this research into human trials, while basic research is progressing more slowly. New devices have enormous potential to help patients whose seizures are not controlled by medication and who are not candidates for curative epilepsy surgery. Further research into where, how, and when to deliver electrical stimulation in the brain is needed to maximize benefit from these new strategies to treat epilepsy. © 2001 Academic Press

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Since the early 1970s there has been interest in implantable devices for treating medically resistant epilepsy. A confluence of ideas and observations over the past several years have led to an explosion of effort in this area, both in academic institutions and in industry. The results of these efforts include implantable cardiac devices for treating dysrhythmias and heart failure, implantable brain devices for treating tremor and Parkinson's disease, basic research identifying neuronal networks and “circuits” related to specific seizure types in animals, the vagus nerve stimulator (VNS) for treating partial epilepsy, and encouraging results from new computational approaches to detecting and predicting epileptic seizures.

In the mid-20th century, Penfield and Jasper observed that the thalamus appeared to play an important role in the generation and spread of seizures.

They developed the concept that a central functional unit, or network of structures, regulated seizure propagation to the cerebral cortex (1). This “centroencephalon,” or central relay area, could theoretically be the target of an intervention, such that interfering with its function might prevent seizures from beginning or spreading. For the next 30 years, a number of investigators published observations that seizures of different types in animal models of epilepsy were likely initiated and propagated from a number of discrete circuits (2, 3). One region, called “area tempestus” by Gale, caused rapid generalization of epileptiform discharges when activated. At the same time, improvements in epilepsy surgery, guided by high-resolution structural and functional neuroimaging, suggested that partial-onset seizures could be eliminated by focal cortical resection, particularly in temporal and lesional extratemporal epilepsy. Success in this approach raised the possibility that seizures could be eliminated by disrupting function in these regions in ways other than removing tissue, which would lower morbidity. An example is the technique of multiple subpial transection (MST), in which horizontal corticocortical con-

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nections are disrupted surgically to inhibit synchronization (4, 5). While MST has enjoyed some success in functional epilepsy surgery as a palliative procedure, it can generate significant morbidity from tissue injury. Still, the success of this less invasive surgical method helped set the stage for therapies causing reversible functional disruption through local drug infusion or electrical stimulation.

The observation by Spencer and Spencer in 1996 that partial-onset seizures frequently terminate abruptly, with a transition from synchronized, broad-field rhythmic activity to focal and sometimes global suppression of the EEG, has stimulated research into locally delivered seizure therapy (6). Under the presumption that intervention in the region of the epileptic focus or more central, networked structures capable of triggering these responses may be effective in suppressing seizures, much of the current research has been devoted to searching for these regions and for the best stimulation algorithms or locally delivered drugs to activate them.

The success of stereotactic surgery and implantable electrical stimulation devices for treating movement disorders, primarily Parkinson's disease and tremor, is among the most powerful forces pushing antiepileptic devices as a viable form of local seizure therapy (7a). These devices modulate network function by inhibiting neuronal firing in deep brain nuclei via high frequency electrical stimulation (e.g., ≥ 130 Hz) (7b). The functional anatomy of these networks has been mapped in experimental models, which has yet to be accomplished for epilepsy (8, 9). Case series have been published, and larger, blinded, controlled trials to demonstrate efficacy and clearly define morbidity and mortality related to brain stimulation for movement disorders are underway (10). Deaths from intracerebral hemorrhage related to electrode implantation have been reported (11). Despite these rare events, excellent short-term results from pilot trials, accentuated by high-profile demonstrations of patients "frozen" by Parkinson's disease who are suddenly able to run across the room at the flick of their stimulator switch, are providing powerful stimuli for investment into research on epilepsy devices. Finally, there is great economic incentive for device companies to expand the uses of their neural stimulators to epilepsy. The very large number of potential candidates for such treatment in the United States alone suggests that such technologies would be commercially successful.

The main challenge to investigators in developing epilepsy devices is in mapping the circuits and networks involved in seizure generation and modulation

to be able to determine where, how, and when to intervene to generate effective therapy. This challenge must be addressed in the context of carefully controlled clinical trials to assess efficacy and morbidity related to both surgery and chronic therapy, so that overall risk-benefit relationships can be objectively assessed.

ANIMAL MODELS OF BRAIN STIMULATION FOR SEIZURES

Suppression of various types of seizures using electrical stimulation has been demonstrated in a number of animal models of epilepsy. Stimulation targets associated with antiepileptic effects in animals include the subthalamic nucleus (12), the anterior thalamic nucleus (13, 14), the hypothalamus (15), mamillary bodies (13), cerebellum (16), basal ganglia (17, 18), locus ceruleus (19), and substantia nigra (20). In addition, stimulation of the vagus nerve in dogs (21) and the trigeminal nerve in rodents (22) has also been demonstrated to reduce or abort experimental seizures. *In vitro* experiments in hippocampal slice models of epilepsy have demonstrated efficacy in arresting epileptiform activity and seizures through the application of electrical stimulation (23) and magnetic fields (24, 25). In this limited model, however, the potential and methods for translating these techniques to humans are less clear. Sorting out which stimulation targets, if any, may be effective in which type(s) of human epilepsy is a significant undertaking, and will require meticulous investigation as the physiologic foundations for designing epilepsy devices are constructed.

HUMAN TRIALS

Based on the animal literature, a number of early investigational clinical trials of brain and peripheral nerve stimulation in humans have taken place, most of which have not been controlled or blinded studies. These have included trials of cerebellar stimulation (26–28) and centromedian thalamus (29a) and periodic hippocampal stimulation (29b). These studies have demonstrated reasonable safety of the technology, tolerability of chronic, in-dwelling electrodes, and encouraging preliminary results, though not sufficient to support an application to the Food and Drug Administration for approval. The two double-blind, con-

trolled trials of brain stimulation for epilepsy published to date have been significantly less encouraging, demonstrating low efficacy for cerebellar (30a) and centromedian thalamus stimulation (33), though some patients reported great benefit. These studies used intermittent, “blind” stimulation, in which stimulators were turned on and off at regular intervals, independent of the patient’s state or proximity in time to seizures.

In 1999, Lesser *et al.* studied focal stimulation in the region of the seizure onset zone as potential therapy for epilepsy (30b). They provoked rhythmic afterdischarges during stimulation mapping of cortical function prior to epilepsy surgery via subdural electrodes and attempted to terminate this evoked synchronous activity with electrical stimulation. In this study, short-duration, bipolar current pulses applied to the region generating the afterdischarges suppressed afterdischarges. In some cases this “counter” stimulation was felt to prevent clinical seizures from occurring. This was one of the first studies in humans demonstrating the efficacy of reactive or “intelligent” brain stimulation in the region of the epileptic focus as a means of suppressing seizures. These results are encouraging but should not be overstated, because the relation between afterdischarges and spontaneous clinical seizures is not clear.

BLIND VERSUS INTELLIGENT DEVICES

Two basic therapeutic paradigms of electrical stimulation are currently under investigation for treating epilepsy. “Blind” devices stimulate in repetitive cycles in timed “on” and “off” periods, without any attempt to measure or react to changes in the physiology, i.e., the EEG, of the patient. The exact nature and timing of these cycles are largely empirical at this point, patterned after older devices in which stimulation parameters were based more on hardware limitations than physiologic considerations. The advantages of cyclical stimulation include the need for only elementary computational circuitry and no monitoring algorithms, prolonged battery life, and predictable stimulation-related side effects, as there is no freedom for the device to alter output other than by manual adjustment. There is evidence of cumulative physiologic and therapeutic effects related to periodic stimulation that build over time and can persist for days, weeks, or even months after cessation of stimulation (31, 32), including therapeutic effects of vagus nerve stimulation over time (31), persistent metabolic changes in

deep structures after stimulation (33, 34), and therapeutic effects in patients with movement disorders that outlast the duration of stimulation.

Intelligent brain stimulators that are capable of detecting and predicting epileptic seizures are currently under development. Eder and co-workers used a simple seizure detection algorithm to trigger infusion of a benzodiazepine into the epileptic focus soon after seizure onset in a rodent, which successfully suppressed seizure development and spread (35). Similarly Fanselow *et al.* were able to trigger trigeminal nerve stimulation to a simple amplitude-frequency detector to abort pentylenetetrazol-induced seizures in rats (22). Encouraging results for accurate seizure detection with relatively short seizure detection delays have been reported by Osorio *et al.*, though the performance of this system may be somewhat artificially enhanced, as the same data were used to both train and test the algorithm (36). Several research groups, including ours, have demonstrated reproducible “fingerprint” patterns in quantitative measures of seizures from individual subjects, suggesting that seizure detection, and perhaps prediction performance, can be enhanced by training on the neurophysiological data from individual patients (37, 38, 39).

CURRENT TRIALS AND CLINICAL RESEARCH

At present, most clinical research with regard to implantable brain devices for treating epilepsy consists of safety and feasibility pilot studies. Most of this research is being performed under Investigational Device Exemptions (IDEs) from the FDA and focuses on periodic stimulation in nuclei in and around the thalamus and in the region of the epileptic focus. A number of academic centers involved in this activity worldwide have found encouraging safety and tolerability results, though too few patients have been implanted to demonstrate efficacy. An NIH-funded study of anterior thalamic nucleus stimulation for refractory partial epilepsy is set to commence later this year under the direction of Robert Fisher, M.D., Ph.D., from Stanford University. Figure 1 depicts placement of stimulating electrodes in the anterior thalamic nucleus on brain MRI in one patient implanted with an anterior thalamic nucleus stimulator during a pilot study to assess safety, tolerability, and optimal stimulation parameters for this form of treatment at the University of Pennsylvania.

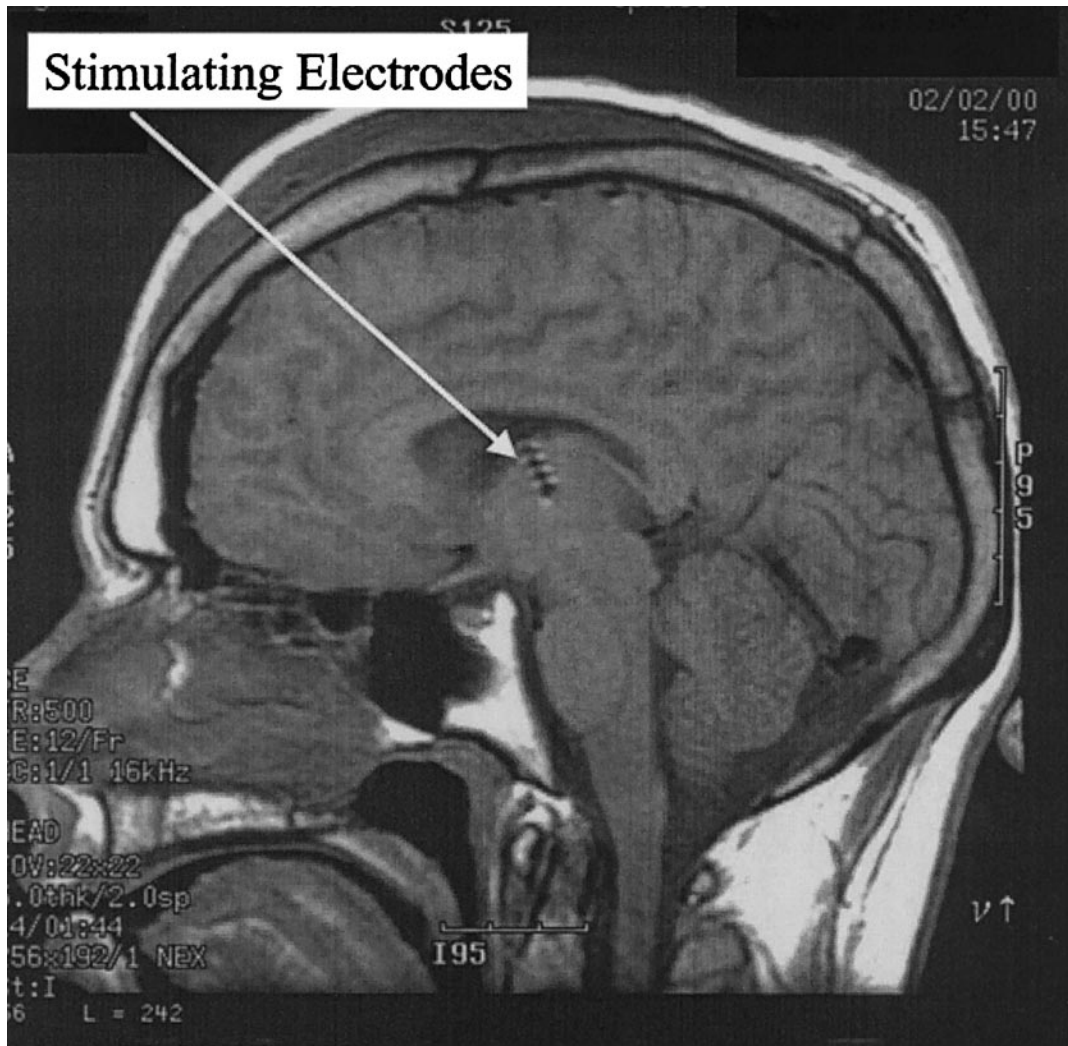


FIG. 1. Sagittal MRI scan of a patient implanted with stimulating electrodes in the anterior thalamic nucleus. Note that the image of the electrode contacts on the scan artifactually overestimates their size.

SEIZURE DETECTION, PREDICTION, AND CLOSED-LOOP DEVICES

The discovery of seizure precursors that may make it possible to predict epileptic events far enough in advance of electrical and clinical onset to allow abortive treatment has fueled collaboration between epileptologists and quantitative scientists in engineering, physics, and applied mathematics. Several research groups have demonstrated changes in quantitative parameters in anticipation of seizure onset. Several of these groups use methods based on nonlinear dynamics, such as tracking the principal Lyapunov exponent (40, 41), a form of low dimensional chaos (38, 42, 43),

and a derivation of correlation dimension, called “neurocomplexity loss (39, 44, 45).” The work of these investigators has changed how neurophysiologists look at the pre-seizure period, suggesting that seizures may develop over longer time frames than was previously thought. More recently, our group has identified a cascade of events in intracranial EEG recordings obtained from patients with refractory mesial temporal lobe epilepsy undergoing evaluation for epilepsy surgery (46). These events consist of a series of changes in quantitative measures of brain activity that occur over 7 hours or longer in some patients; further, the progression corresponds to increasing probability of seizure onset.

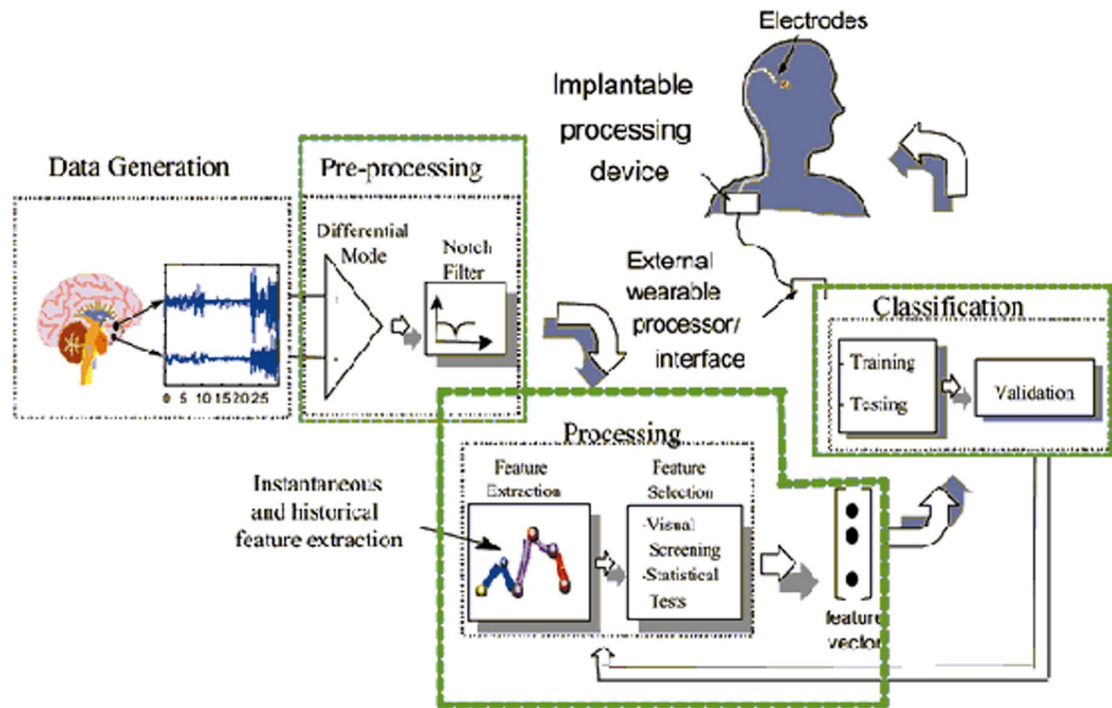


FIG. 2. Schematic of the steps in processing, training, and validation of a seizure prediction algorithm developed in our laboratory. This algorithm uses a library of quantitative features, which are optimized and tailored to the individual patient. Processing is performed by a programmable unit that buffers and transmits historical intracranial EEG data, as well as processes brain signals in real time.

There are a number of ways that “closed-loop” algorithms can be implemented in implantable seizure treatment devices. In “deterministic systems,” a processing system monitors EEG from electrodes implanted in the substance or on the surface of the brain for a specific pattern or change, usually in one parameter, and then triggers brain stimulation in the focus or another more central region to stop the seizure. Algorithms in such systems must weigh trade-offs between rapidity of seizure detection (measured by the delay in time from electrical seizure onset until the system identifies the seizure), sensitivity, and selectivity. A theoretical concern with such systems is that delaying therapeutic action until electrical seizure onset may be too late to contain seizures and prevent clinical symptoms. In “probabilistic systems,” a variety of parameters are measured that estimate the probability of seizure onset in a variety of time frames. Therapeutic intervention is then applied in an escalating fashion, beginning with less invasive paradigms, progressing slowly with stronger and potentially more disruptive stimuli as seizures become more likely, up to maximal therapy at the time of imminent seizure onset. These systems can tolerate a higher false-positive rate of

seizure prediction, provided that the mild interventions triggered at low probability of seizure onset are benign and do not induce side effects. In addition, when these systems use multiple electrode sensing sites, prediction and treatment algorithms can be programmed to monitor the spatial spread of seizure precursors and expand the sites of intervention accordingly to prevent recruitment of a sufficient volume of tissue to trigger clinical events.

Figure 2 displays the steps required for setting up and training a closed-loop probabilistic seizure prediction and/or therapeutic system such as the one we have designed in our laboratory. Intracranial EEG is digitized; quantitative features are extracted from these waveforms and tested, and a feature vector is selected, composed of those features from a broad library of measurements that best predict seizures in the specific patient. An artificial intelligence structure—in this case, a wavelet neural network—is trained on the pre-seizure patterns of a specific patient and then tested on a number of seizures not previously used for training. The device is then put “on-line” after implantation in the patient, and a set of probabilities of seizure onset are generated in real

time. Interventions are triggered as necessary, following changes in long- and short-term probabilities of seizure onset, culminating in high-amplitude electrical stimulation over a wide area at the time of seizure onset, if clinical seizures are not prevented by pre-seizure stimulation (46). The device is periodically retrained, as patient-specific patterns may be altered over time in individual patients. Further research into these systems is actively being pursued in animal models of epilepsy in our laboratory and by other groups in the United States and Europe. As a by-product of this activity, it is likely we will learn more about the mechanisms underlying the quantitative electrophysiologic changes that precede seizures, which may ultimately result in even better targeted therapies to prevent seizures, perhaps in the form of medications or stereotaxic surgical procedures.

CONCLUSION

Implantable devices for treating medically refractory epilepsy are likely to become available over the next decade. The main challenges to be solved are localizing the correct regions to stimulate or in which to infuse drugs, and determining the best parameters for electrical stimulation and the optimal time to deliver therapy. Perfecting the stimulation algorithms and implementing them in real time, on slow, power-conserving implantable hardware platforms presents a significant challenge for sophisticated signal processing tasks. Finally, while partnerships with industry are vital to the success of this type of costly, labor-intensive research, it should be remembered that clinical trials of seizure devices must be based on a sound scientific foundation and well-designed studies.

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