PREDICTION AND CONTROL OF EPILEPTIC SEIZURES: THE BASIS FOR BRAIN PACEMAKERS IN EPILEPSY

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Abstract: Epileptic seizures are manifestations of epilepsy, a serious neurological disorder second only to stroke. Prediction of seizures from real-time analysis of the EEG is now almost a reality. As the ability to predict leads to the possibility of control, research in control of seizures is expected to flourish in the near future, much to the benefit of the epileptic patient. Investigations in stimulation and control of the brain have attracted the attention of the academic community, and medical device companies have started off designing and implementing intervention devices for various neurodegenerative diseases. These devices will be the brain counterparts to cardiac pacemakers and defibrillators. Electromagnetic stimulation and /or administration of anti-epileptic drugs upon the issue of a warning for an impending seizure may significantly reduce the number and severity of epileptic seizures. The devised control schemes should be power efficient, with maximum efficacy and minimum side effects. The expectation is that a combination of real-time seizure prediction technology with feedback control techniques would result to a novel and effective treatment for epilepsy. Furthermore, if successful, the thus derived control schemes and theories may be applied to Parkinsonian tremors, sleep disorders, migraines and other brain dynamical disorders with intermittent symptoms.

Introduction

Epilepsy is considered the window to the brain's function, and an increasingly active, interdisciplinary field of research [1]. The "sacred" or "divine" disease is among the most common disorders of the nervous system, second only to stroke, and affects approximately 1% of the world's population [2]. While epilepsy occurs in all age groups, the highest incidences occur in infants and the elderly [3]. The high incidence of epilepsy stems from the fact that it occurs as a result of a large number of causes, including genetic abnormalities, developmental anomalies, febrile convulsions, as well as brain insults such as craniofacial trauma, central nervous system infections, hypoxia, ischemia, and tumors.

The hallmark of epilepsy is recurrent seizures. The seizures are due to sudden development of synchronous neuronal firing in the cerebral cortex and are recorded by electrodes on or inside the brain. Electroencephalographic (EEG) recordings from the epileptic brain [4] show that the epileptoform discharges may begin locally in portions of the cerebral hemispheres (partial / focal seizures, with a single or multiple foci) or begin simultaneously in both cerebral hemispheres (generalized seizures). After a seizure's onset, partial seizures may remain localized and cause relatively mild cognitive, psychic, sensory, motor, or autonomic symptoms, or may then spread to cause altered consciousness, complex automatic behaviors, or bilateral tonic-clonic (convulsive) movements. Generalized seizures cause altered consciousness at the onset and are associated with a variety of motor symptoms, ranging from brief localized body jerks to generalized tonic-clonic activity. Seizures come and go, in a seemingly unpredictable way. In some patients, seizures can occur hundreds of times per day; in rare instances, they occur only once every few years.

If seizures cannot be controlled, the patient experiences major limitations in family, social, educational, and vocational activities. These limitations have profound effects on the patient's as well as on his or her family's quality of life [5]. In addition, frequent and long, uncontrollable seizures may produce irreversible damage to the brain, status epilepticus offering supporting evidence for such a hypothesis [6]. However, it still is not clear if seizures are the cause or the result of such a damage that worsens over time if left untreated [7]. It is a widely held view that seizures from mesial temporal structures may arise because of damage to hippocampal circuitry (e.g. hippocampal sclerosis). Loss in neurotransmitter receptors in the hippocampus also has been reported [8]. Physiological studies in epileptogenic hippocampi have demonstrated loss of neuronal inhibition. It is generally believed that impairment of the balance of inhibition and excitation at the neuronal network level is one critical factor for epileptogenesis [9-11].

The mainstay of treatment of epilepsy today is pharmacological. Anticonvulsant drugs are taken daily, in fixed doses, titrated to achieve a steady-state concentration in the blood. The specific concentration is chosen to provide the most effective seizure control with the least degree of side effects. Nonetheless, approximately 33% of patients with epilepsy have seizures that are refractory to medical therapy. For these patients, surgical treatment may be an option.

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Surgical treatment can be effective in carefully selected cases, which usually represent 8% of the total epileptic patients [12]. Good responses (Engel Class I) to surgery occur in approximately 70 to 90% of patients with complex partial seizures due to mesial temporal sclerosis. However, the response rate drops off markedly in patients with epileptogenic lesions of the neocortex (most commonly in frontal or temporal lobes). Patients with more than one epileptogenic focus, or those with generalized seizures, usually do not experience complete seizure control with current surgical therapy. Side effects from both surgical and pharmacological treatments have been reported. One problem with chronic daily dosing with anticonvulsant drugs is that many patients develop a tolerance to the anticonvulsant effect. Surgery, on the other hand may inflict damage to other brain functions, depending on the proximity of the focus to related brain centers.

For many years, there have been attempts to control epileptic seizures through another modality, the electrical stimulation of the brain [13]. Attempts to control medically intractable seizures with cerebral stimulation were undertaken in the 1960's, but were largely abandoned after 1970's, due to relatively lack of efficacy. Recently, chronic vagus nerve stimulation (VNS) was approved for clinical treatment of intractable seizures [14-15]. Clinical outcomes with both direct brain stimulation and vagus nerve stimulation suggest that these methods carry a much lower incidence of the adverse cognitive, neurological, and systemic effects that occur with anticonvulsant drugs [16] and lend credence to the idea that stimulation could become a highly effective and well-tolerated way of treating seizures. However, the overall efficacy of existing techniques has been modest. For example, in the pivotal studies of the vagus nerve stimulator, perhaps 35-40% of patients experienced a 50% decrease in seizure frequency, and a much smaller number became seizure free [17].

Furthermore, the mechanism for the anticonvulsant effect of electrical stimulation is still unknown, although many theories have started to develop. Chkhenkeli et al. reported inhibitory effects of electrical stimulation at the head of the caudate nuclelus, cerebellar dentate nucleus, thalamic centromedian nucleus and neocortical and temporal lobe mesiobasal epileptic foci in 150 patients [17]. Suppression of subclinical epileptic discharges and a reduced frequency of generalized, complex partial, and secondary generalized seizures was noted with stimulation of 4-8 Hz in the head of the caudate nucleus and with 50-100 Hz in the cerebellar dentate nucleus. Centromedian nucleus (CM) stimulation at 20-130 Hz desynchronized the EEG and suppressed partial motor seizures. Direct stimulation of the epileptic focus at 1-3 Hz may suppress rhythmic after discharges (ADs). Yamamoto reported similar inhibitory effects on ADs as a result of low frequency stimulation of the epileptic focus [18]. Similar suppressive results by Kerrigan et al. were observed with 100 Hz stimulation of the anterior thalamic nucleus [19]. Patients clinically and statistically improved with respect to severity of their seizures.

Clinical trials of deep brain stimulation (DBS) for epilepsy management have recently been started in the United States, one being conducted by Medtronics and the other by NeuroPace [19-20, 21]. In both cases, surgical implantation of stimulating electrodes is required. Like the VNS device, the DBS device is programmed to deliver intermittent stimulations independent of the presence or absence of seizure activity, thus possibly interfering with the normal function of the brain. The current DBS devices may conceivably detect a seizure after its onset, and then attempt to abort it by delivering an electrical stimulation, thus serving as a brain defibrillator [22]. A major conceptual improvement over both of these approaches would be if stimulation is activated early enough to even prevent the seizure from occurring, thus to serve more like a brain pacemaker. This would require the ability to detect EEG changes predictive of an impending seizure before the seizure develops. Even better would be a paradigm that utilizes continuous feedback control algorithms to maintain the brain electrical activity in a non-seizure state.

From the engineering point of view, in the last few years, we have started viewing and investigating epilepsy as a dynamical disorder of the brain. Preliminary results, along this line of research, indicate that at least seizures of some type are predictable long prior to their occurrence. Importantly, these results are coming from analysis of patients with seizures not necessarily preceded by auras.

As the ability to predict leads to the possibility of control, research in controlling of seizures is expected to flourish in the near future, much to the benefit of the epileptic patient. Investigations in stimulation and control of the brain have attracted the attention of the academic community, and medical device companies have started off designing and implementing intervention devices for various neurodegenerative diseases (e.g. stimulators for Parkinsonian patients) as counterparts to the existing ones for cardiovascular applications (e.g. cardiac pacemakers, defibrillators).

In this paper, a brief historical perspective is presented, with main references from the field of seizure prediction and seizure control. Current trends and potential problems are highlighted. It is generally expected that application of seizure prediction technology and adaptive control to the epileptic brain will lead to the first brain pacemakers for epilepsy (and other brain dynamical disorders) in the near future.

Historical Perspective

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 [23]. However, theories based on reports from clinical practice and scientific intuition, like the "reservoir theory" postulated by Lennox [24], existed and pointed out to the direction of seizure predictability. Various feelings of auras, that is, patients' reports of sensations of an upcoming seizure, exist in the medical literature. Penfield [25] was the first to note changes in the cerebral blood flow prior to seizures. Deterministically predictable occurrences of seizures (reflex seizures) in a

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small minority (about 3 to 5%) of epileptic patients are reported as a result of various sensory stimuli [26]. These theories and observations provided initial evidence that seizures might be predictable.

While seizures are the major hallmark of epilepsy, interictal (between seizures) spikes in the EEG that result from intermittent synchronization of a large number of cortical neurons are the other electrographic hallmark of epilepsy. Epileptic spikes are indicative of a pathological hypersynchrony in the brain that could be provoked by paroxysmal depolarization shifts (PDS) of the resting potentials of epileptic neurons and be facilitated by increased excitation and/or decreased inhibition in the neural networks involved [27]. At this microscopic level, a theory of neuronal recruitment, as a necessary condition for an epileptic spike to occur, was developed. Short times in the order of tens of msec were postulated, in agreement with the observed duration of epileptic spikes. Intensive research efforts via computer analysis of epileptic spikes in the EEG were undertaken, as it was assumed that localization of spikes could answer the question of the location of the epileptogenic focus in patients with focal epilepsy [28]. To test the hypothesis of neuronal recruitment at the macroscopic level for a seizure to occur new research was launched. It was hypothesized that spikes should occur more frequently during the preictal (before a seizure) than the interictal (between seizures) or postictal (after a seizure) periods. This theory was not substantiated as rate of spike occurrences was found not to change significantly before and after seizures [29].

In 1983 the first paper reporting consistent changes of spike activity prior to seizures appeared [30]. Lange et al. at UCLA showed that it was the spatial patterns of spikes across brain sites, and not the rate of spikes per brain site, that were progressively changing prior to seizures. These results were qualitatively in agreement with previously reported results from animal experiments [31].

The 80s saw the emergence of new signal processing methodologies based on the mathematical theory of nonlinear dynamics, in particular the spontaneous formation of organized spatial, temporal or spatio-temporal patterns in various physical, chemical and biological systems [32-34]. These techniques quantify the signal structure from the perspective of dynamical invariants (complexity of the attractor quantified by its correlation dimension, or divergence of trajectories by the largest Lyapunov exponent), and were a drastic departure from the signal processing techniques based on the linear model (Fourier analysis). Nonlinear dynamical algorithms were also applied to biological systems, notably the heart and brain (EEG) [35, 36]. In 1988, Iasemidis and Sackellares reported the first application of nonlinear dynamics to clinical epilepsy [37]. This group started to analyze continuous, multichannel, preictal, ictal and postictal EEG from epileptic patients with temporal lobe epilepsy, devising new and modifying existing measures from the theory of chaos to quantify the rate of divergence of trajectories (Lyapunov exponent) for the analysis of EEG in epilepsy. The central concept was that seizures represented transitions of the epileptic brain from its "normal", less ordered (chaotic) state to an abnormal, more ordered state and back to a "normal" state along the lines of chaos-to-order-to-chaos spatiotemporal transitions. The Lyapunov exponents were chosen because they can measure chaos and stability of general states of linear or nonlinear systems.

This dynamical modeling hypothesis changed some long-held beliefs about seizures. Iasemidis and Sackellares reported the first evidence that the transition to epileptic seizures may be consistent with a deterministic process [38], [39] and that the EEG during epileptic seizures can be better modeled as an output of a nonlinear than a linear system [40]. The existence of long-term preictal periods (order of minutes) was shown using nonlinear dynamical analysis of EEG from subdural arrays, and raised the feasibility of seizure prediction algorithms by monitoring the temporal evolution of the short-term Lyapunov exponents (STLmax) at critical brain sites [41]. The possibility of focus localization and seizure detection was also reported with the same technique in 1990 and 1994 respectively [42], [43]. Elger and Lehnertz modeled the spatio-temporal dynamics of the epileptic focus in 1994 [44], while Scott and Schiff directed attention to the time structure of inter-ictal spikes [45]. Lopes da Silva et al, who had been developing neurophysiology driven dynamical models for EEG activity since the late 70s, also quantified state bifurcations in epileptogenesis [46]. Hively et al applied "chaos methods" to the prediction of epileptic seizures [47], while Lerner used the correlation integral to track changes in the EEG [48]. Pezard et al utilized several nonlinear measures, including entropy, to track EEG changes [49]. Other groups [49-58] followed towards the detection of the preictal period. The important conclusion from all the different techniques tried so far is an accumulation of evidence that there are measurable differences in the EEG prior to seizure onset that can be exploited for epileptic seizure prediction. In parallel, statistical evaluations of the proposed seizure predictability schemes, with respect to their sensitivity and specificity, have been developed [59-65].

In the meantime, Iasemidis and Sackellares groups further improved the STLmax technique with the use of optimization techniques and the critical mass hypothesis for selection of the most relevant (critical) electrode sites prior to seizures. They applied the algorithm to continuous, long (days) EEG data from depth, subdural or scalp recordings in patients with temporal lobe and frontal lobe epilepsy. The first prospective seizure prediction algorithm that ran on continuous EEG data, in real-time and on-line was published in 2003. The reported sensitivity and specificity values of that algorithm were high in both patients and animal models, with average prediction times in the order of 70 minutes prior to seizures [66-69]. A series of other recent papers by these groups offer hints for further improvement of this first seizure prediction algorithm [70-84].

The emerging view from the above investigations is that seizures are manifestations of recruitment of brain sites in an abnormal hypersynchronization. The onset of such recruitment occurs long before a seizure and progressively culminates into a seizure. Therefore,

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seizures appear to involve a progressive coupling of the focus with the normal brain sites during a preictal period that may last days to tens of minutes. Thus, auras could be defined as the late stage of this emerging activity. Reflex seizures may be viewed as results of input stimuli capable of inducing a fast preictal dynamical recruitment.

Recent and old research with brain electrical stimulation [85-95] point out to a series of problems that need to be addressed for successful control of seizures, namely the number of stimulating electrodes, number of recording electrodes, brain areas to be stimulated, characteristics of stimulation, side effects expressed as damage to the brain tissue or function, issues of economy (e.g. battery life of the stimulator(s)) etc. It appears that a combination of seizure control technology and seizure prediction technology may solve some of these problems.

Conclusion

The ability to predict and control epileptic seizures well prior to their occurrences may lead to novel diagnostic tools and treatments of epilepsy. Evaluation of old and new anti-epileptic drugs and protocols, with respect to duration of patients' seizure susceptibility and/or preictal periods detected by seizure prediction algorithms, may lead to the design of new, more effective antiepileptic drugs. Electromagnetic stimulation and /or administration of anti-epileptic drugs at the beginning of the preictal period to disrupt the observed entrainment of normal brain with the epileptogenic focus may result to the development of the first brain pacemakers for epilepsy in the very near future.

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