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Seizure Prediction 6: From Mechanisms to Engineered Interventions for Epilepsy

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Introduction

Epilepsy is a common neurological disorder that affects nearly 1% of the world's population, and is characterized by the occurrence of recurrent spontaneous seizures. The apparent unpredictability of seizures is both a hallmark of the disorder and one of the

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Patient's Perspective

Aatif M. Husain, M.D., Editor-in-Chief Journal of Clinical Neurophysiology

Dear Dr. Husain, The Alliance for Epilepsy Research (AER) was honored to host the Sixth International Workshop on Seizure Prediction (IWSP6) held in San Diego, California this past November, and I was honored to be a member of the Organizing Committee. This is the second time around for both of us; we hosted and organized for IWSP4 in Kansas City in 2009.

I cannot say enough good things about the people who attend and participate in these conferences. In the meeting rooms the brain power is palpable! Many, many of us who have epilepsy are heartened that they, and others around the world, are focused on understanding and treating epilepsy in new and different ways by using technology, mathematics, engineering, and physics.

In my work with AER I often receive calls and emails, occasionally from epilepsy patients but most often from family members of people who have intractable epilepsy. They are desperately looking for help, which tells me current treatments are lacking. I tell them about the incredible work being done in the seizure prediction arena, and immediately, without a moment's hesitation, they ask if there is a need for study subjects. They have been through it all without much success, but will not give up. The IWSP series of workshops offers much needed hope.

By conservative estimates there are 60 million people in the world who have epilepsy and the vast majority do not have complete control of their seizures. The unpredictability of their seizures keeps them at home, unemployed or under-employed, isolated and dependent. For many the treatments are debilitating in their own right and further compromise quality of life.

The seizure prediction workshops and the ongoing work of the researchers are rays of hope for those trapped in the world of epilepsy. Of course, the ideal goal is a cure for epilepsy. Until then, we look at the knowledge, networking, and collaborations that are facilitated by IWSP and are optimistic that seizure warning/prediction and automated interventions triggered by warnings are within reach.

My compliments and encouragement to all!

Sincerely

Susan Arthurs, Chair Alliance for Epilepsy Research

primary factors contributing to the degradation in quality of life and increased potential for accidental injury (Arthurs et al. 2010). Unpredictability also increases the difficulty of achieving good seizure control. Patients with uncontrolled seizures have been shown to have increased risk of comorbid conditions that include sudden unexplained death in epilepsy (SUDEP), and increases the overall burden of the disorder on family members and caregivers.

In November of 2013 we had the opportunity, along with Björn Schelter and Susan Arthurs, to organize the Sixth of the International Workshops on Seizure Prediction (IWSP). This is an interdisciplinary gathering of engineers, physicists, mathematicians, epileptologists, neurosurgeons and neuroscientists, self-termed the International Seizure Prediction Group (ISPG). The goals of the ISPG are to bring quantitative and technological approaches to addressing the prediction and control of epilepsy.

There are two widely quoted targeted products from seizure prediction. First, successful seizure prediction enables development of devices and strategies for seizure intervention and improvement in quality of life. A simple advance warning of a high likelihood of a seizure can potentially enable a person with epilepsy to avoid situations that might place themselves or others at risk.

Second, reliable and accurate seizure prediction would result in useful insights into the mechanistic underpinnings of seizure generation and related brain activity abnormalities. In particular, these may enable us to accomplish the “holy grail” of epilepsy treatment: focal seizure prevention to minimize the cognitive, behavioral and quality of life effects from both the treatments and the seizure events. We expect that articulating these and placing them into the context of human seizures and EEG recordings will increase the chances that the twin goals of seizure prediction and technology-based development of new prevention strategies will be realized.

The IWSP series was initiated at the beginning of this century as a platform within which the ISPG can exchange ideas and identify high priority avenues for future investigation, with progress documented in summaries following each meeting. Thus, these meetings and their output serve a similar role as the formal Epilepsy Benchmarks (Kelley et al. 2009), to which many ISPG members have contributed.

By way of introduction, we provide here a short history of seizure prediction from the last century leading up to the birth of the IWSP series, followed by a summary of the identified goals as emerging from the previous IWSPs. We then outline the significant achievements made in seizure prediction and the future goals of the ISPG as further detailed in the invited reviews. We close with an attached letter from Susan Arthurs, IWSP6 co-organizer and Chair of the Alliance for Epilepsy Research, which provides a patient’s perspective on the import of this research.

Seizure Prediction and Instrumented Seizure Control through the Last Century

Seizure prediction involves identification of patterns from physiological features that precede seizure events. The history and advances of such efforts can be understood in the context of co-developing technologies, brain science, and clinical standards of care. But as often as not, advances in one realm lead to temporary abandonment of an otherwise promising approach, followed by its rediscovery. One such clearly identified pattern is the relationship between behavioral and sleep cycles, time of day, and seizure event rates (Gowers 1881).

Prior to the widespread adoption of EEG technology for clinical neurological diagnosis, patterns were extracted from patient records from large clinical practices and especially institutions for housing persons with epilepsy. In a study of over 2500 seizures from 64 patients, Mary Langdon Down and W. Russell Brain (Langdon-Down and Russell Brain 1929) found time of day dependence of seizure timing in nearly 70% of patients: 24% of patients had high nocturnal seizure propensities with seizure rates peaking between 10 and 11PM and again between 2 and 3 AM; and 43% of patients had high diurnal seizure propensities, with a strong peak seizure rate between 8 and 9 AM, with secondary peaks between 3 and 4 PM and again between 7 and 8 PM. When interpreted in terms of sleep cycles, they observed that seizure rates peak roughly 2 hours prior to normal wake times in 35% of patients, and in an hour-long period starting roughly a half-hour after waking in 24% of patients. Griffiths and Fox (Griffiths and Fox 1938) found longer duration patterns in a study of multi-year to decades long patient records. Monthly clusterings were observed in both men and women, along with other distinct pattern periodicities including bi-weekly, bi-monthly, 3.5 monthly, etc. Extremely long emerging patterns included a boy who had one seizure per year, always in March, and a pair of sisters with a distinct two-year cycle.

Once the technology for neural electrical recordings became widespread, the search for preictal EEG patterns began. One such pattern was the rate and quality of paroxysmal epileptiform discharges or spikes, observed in acute penicillin-induced animal models of seizures (Ralston 1958) and spontaneous human recordings (Ralston and Papatheodorou 1960). The advent of telemetric recordings in the late 1960s, comprising what we now think of as a very few channels, and analog telemetry to chart recorders and analog magnetic tape, provided the opportunity to investigate brain electrical activity patterns over long periods. An early report by Stevens et al. (Stevens et al. 1971) utilizing automated seizure and interictal spike detection from day-long recordings confirmed that both ictal and interictal spikes were time of day dependent, and demonstrated that the interictal spike rate was behavioral state dependent. But to connect Ralston's findings to spontaneous human epileptic seizures required more data. Gotman et al. (Gotman et al. 1982) quantified changes in spike rate over minutes, hours and days preceding the observed seizures from 11–18 day long clinical intracranial EEG recordings. They reported that *when corrected for state of vigilance* “spiking rates were clearly increased in the hours and days following almost every seizure and the return to baseline following this increase could take several days” but that “no changes were observed in the minutes preceding seizures.”

As EEG technology developed, the promise of feedback electrical control was envisioned. One of the earliest patents was a method in which bio-state is measured and fed back to a control state (Eaton 1945). This was quickly followed by a patent application from R.G. Bickford of Research Corporation for a system to automatically administer drugs based on biopotential recordings (Bickford 1954). Although primarily targeted for EEG-based anesthesia dosing, the patent explicitly described its potential for feedback application of anticonvulsants for treatment of status epilepticus. These were followed in the next decade by several applications for automated EEG analysis with applications ranging from anesthesia control (Condict 1970) to epilepsy syndrome diagnosis and seizure focus localization (Roy and Laupheimer 1972). Of particular note is the 1973 patent issued to Saul Liss (Liss 1974) for a method and apparatus to detect pre-seizure electrical activity in mammalian brain and apply control signals to automatically reduce or eliminate such activity.

One of the earliest references to seizure *prediction* in the literature is the published abstract on a joint effort between the Departments of Neurology at UCLA and UCSF and the McDonnell Douglas Astronautics Company to validate the *concept* of predicting major motor seizures using automated spectral-based analysis of two-channel continuous clinical EEG recordings (Viglione and Walsh 1975). This work resulted in a patent application for an automated system to warn of impending seizures (Kesler et al. 1975). However, success in predicting seizures reliably was elusive as there is no documented success or even quantification of results.

Rogowski et al. provide one of the earliest quantitative seizure prediction studies utilizing clinical data (Rogowski et al. 1981). Their work featured long-term 8-channel video EEG from 12 patients recorded to magnetic tape and then subsequently digitized and analyzed with a PDP 11/55 mini-computer. An autoregressive model was applied, and distinct patterns in the regression coefficients were observed in the preictal period, leading to a claim of reliable seizure predictability of at least a few seconds. “The primary cause of generation of the seizures seems to be changes in the ‘parameters’ of the neural system, causing disproportion between excitative and inhibitive mechanisms, and bringing the system into the verge of instability. As long as the system is stable its output depends on the previous and present inputs, whereas the behavior of an unstable system depends on its parameters alone, the input being the energy source for the oscillations.”

Over the next decades, numerous efforts were made to mathematically model the statistics of seizure occurrence (Albert 1991, Hopkins et al. 1985, Iasemidis et al. 1988, Milton et al. 1987). In 1984, Hopkins et al. considered mathematical models of seizure rates as a tool for evaluating pharmacological treatments (Hopkins et al. 1985). They pointed out the inherent Poissonian assumptions usually used, and proposed alternatives to account for clustering and non-stationarities such as time-of-day dependencies. Based on Hopkins’ assertion of multiple susceptibilities based on time of day, Albert proposed an underlying two-state Markov model for the observed Poisson distribution of seizures, and demonstrated an expectation-maximization algorithm for fitting the model parameters to clinical data (Albert 1991). This approach was followed for example by Le et al. who provided a far more efficient computational fitting algorithm (Le et al. 1992). Milton et al. investigated the

statistics of seizure recurrence timing, comparing seizure occurrence patterns with Poisson processes with constant rate (Milton et al. 1987). Their findings indicated that the Poisson pattern could account for only a small fraction of the time-of-day and state of vigilance dependencies and seizure clusters that had been previously documented, indicating that seizure timing is not simply a straightforward random process.

Attention then turned to increasing the sophistication of tools for analyzing and decoding patterns. An early example is the nonlinear dynamical analysis techniques that emerged from the physics and mathematical communities whose theoretical foundation was predicated on low-dimensional deterministic dynamics. Early reports that recordings of seizures might have low-dimensional chaotic structure (Babloyantz and Destexhe 1986) were followed by efforts to use such analyses to predict seizures (Iasemidis et al. 1990). This work attracted the attention of a broad array of researchers spanning the fields of physics, mathematics, neuroscience and engineering, in combination with clinicians involved in treatment of persons with epilepsy. The approaches taken, and their output, are too vast to cover here; the interested reader is referred to reviews such as (Lehnertz 2008, Nagaraj et al. 2015, Wagenaar et al. 2015).

It became clear toward the end of the 1990's that seizure prediction had proved to be a difficult problem, and that validation of potential approaches would require a concerted effort by the interdisciplinary scientific community that had already begun to emerge. In this context, the ISPG and the IWSP series was initiated in order to provide a venue for investigators to come together to discuss the challenges of seizure prediction, provide in-depth and field-specific peer review, and most importantly compete to assess fairly which algorithms would perform best on the same data sets and provide clinically relevant findings.

History of the IWSP and Evolving ISG Goals

The first meeting, in Bonn in 2002, was primarily focused on head to head competition on data sets provided by the participating groups. Reports from the meeting were quite positive (Lehnertz and Litt 2005). Anecdotal reports were slightly more telling: performance of the algorithms on the data sets were highly dependent on the scoring of seizure onset times. More important than these intermediate findings were background discussions on how to organize the ISPG community based on the identified challenges emerging from these discussions. The competition immediately made clear that adequate data was a limiting factor. This spurred an effort to develop shared resources of data sets with standardized annotations.

Another major identified challenge was how to *statistically quantify* seizure prediction and predictability (Mormann et al. 2005). In the most extreme case, the most perfect scoring seizure predictor is one in which a prediction – “seizure is coming” – is initiated at birth, and subsequently at the terminus of each seizure. This predictor is accurate for each predictor over the life of the subject for all but the last prediction, for which death occurs first. But it is both obvious and useless. Similar problems occur with short data sets each of which include a seizure.

The second meeting was held in 2006 on the NIH campus. This workshop focused on core methodological elements identified in the Bonn conference. It included reports on progress from ISG members, but also included guest lectures from a range of other fields involved in prediction on highly complex systems with extreme events such as weather and earthquake forecasting.

The third conference, held in Freiburg, Germany in 2007 (Schelter et al. 2008) sought to bring in both basic mechanisms of seizure generation as well as a seizure prediction contests with strict announced formalisms for quantifying prediction accuracy. The contest featured human recording data sets, part of which was open for training algorithms, and part of which was blinded for quantification of both true and false prediction rates. This meeting made a significant effort to bring in industry representation, in recognition that engineering solutions that include chronic recording, analysis and potentially feedback control would almost certainly require commercial participation to make viable and supported products.

The fourth conference, held in Kansas City in 2009 (Zaveri et al. 2010), was designed to attract a broader participation especially among engineers and clinicians, and dedicated a significant portion of time to didactic sessions for educating clinicians on technical elements such as signal processing and dynamical systems analysis, and for engineers on the basics of epilepsy patient care. These included makers of open and closed loop neurological stimulators as well as those more focused on seizure prediction. Notably, the seizure prediction contest held at IWSP4 yielded no interesting predictions. This resulted in a decision to focus a large fraction of the fifth meeting, held in Dresden in 2011, (Tetzlaff et al. 2013) on quantitative epilepsy and EEG research.

Throughout this evolution of the IWSP series, the ISPG continued to develop and refine core methods for seizure prediction as well as seizure control. These include those that derive from the almost obvious statement that in order to quantify how well a seizure prediction algorithm functions on long data sets, and maybe even to develop such algorithms, one needs such long data sets. In addition, it had become clear by this time that accurate and useful seizure prediction is an exceedingly hard problem, and that despite our commitment, the effort would require a further expansion of the group's knowledge base and tool set. In particular, it became clear that seizure prediction could not be accomplished with mathematical tools and EEG recordings alone, and that neuroscience expertise would be required.

Achievements in Seizure Prediction and Control – report from IWSP6

Aims and design of IWSP6

The Sixth International Workshop on Seizure Prediction was planned as a short satellite meeting to the 2014 Annual meeting of the Society for Neuroscience, in order to encourage new participation, particularly from epilepsy neuroscientists. The topics selected were designed to support the overall goal of seizure prediction. Specifically, speakers and participants were asked to address themes of seizure origin, spread, and termination mechanisms, and the subtleties of how such phenomena are reflected physiological measurements such as EEG. Sessions in the meeting were devoted to neuronal mechanisms

contributing to seizure initiation and spread both from human and animal studies; the complex interactions between seizures and both sleep and autonomic regulatory systems, and how such interactions might contribute to SUDEP; spatial information of seizure networks from human imaging studies; and efforts to use activation to probe epileptic networks. Added to this were reports of major milestones achieved by the ISPG and the broader “engineering in epilepsy” community on seizure prediction and seizure control.

While these questions seem simple, it is rather astounding that so little is known about them, even though 50 years have passed since the neural signature of a seizure (the paroxysmal depolarizing shift) was first described (Ajmone-Marsane, 1964, Goldensohn and Purpura, 1963). Traditionally, epilepsy neurophysiology research has been divided into two camps: a clinical approach that attempts to discern information from EEG recordings on the location and behavior of neural activity, and a laboratory approach that investigates interactions between sites or other physiological structures in simplified models of patterns thought to be important during clinical seizures. By bringing together investigators from both sides of the divide to participate in IWSP6, and focusing attention on the interaction between EEG and neural activity, we hoped to facilitate new collaborations and research directions capable of advancing the field in meaningful ways.

Reports from IWSP6

For this special issue, we have enlisted six groups of IWSP6 participants to provide reviews of the current state of the art and science on a series of topics covered at the meeting and relevant to the development of engineered interventions for epilepsy. All reviews include both junior and senior investigators, and most feature investigators who have not previously, or not recently attended the IWSP series.

The review by Staley et al. Trevelyan et al. (2015) addresses the role of feedforward network inhibition, which is increasingly recognized as a prominent and fundamental cortical response to an incipient seizure. This is followed by a report by de la Prida et al. on the current understanding of high frequency oscillations (HFOs) (Menendez de la Prida et al. 2015). HFOs are of considerable interest to the broader epilepsy community as potential highly localized electrographic biomarkers of epileptic brain, and provide potential to link clinically recognized EEG patterns with the organized neuronal activity that underlies the electrographic seizure.

To date, most of the efforts of the ISPG have focused on neocortical and mesial temporal activity, largely because it is these areas that are sampled during invasive clinical EEG studies. However, it is increasingly recognized that seizures impact functions attributable to subcortical nuclei and pathways. These in turn link both to behavioral and body functions such as consciousness and autonomic function. Similarly, neuroimaging findings and the results of cross-channel EEG correlation suggest that seizures have significant long-range neuroanatomical and functional effects. Not only does this indicate that analysis should be expanded to account for these observations, but the highly significant clinical problems of loss of awareness and SUDEP could benefit from the ISPG’s unique expertise, as reviewed by Sedigh-Sarvestani et al. (Sedigh-Sarvestani et al. 2015).

The article by Grayden, et al. (Kuhlman et al. 2015) provides a view into linking efforts in understanding basic mechanisms of epilepsy and seizure dynamics to the analysis of recorded data and seizure prediction through the use of model-based observation and control techniques.

The remainder of the reviews return to the data sharing and standardization (Wagenaar et al. 2015), and the future of seizure control (Nagaraj et al. 2015). Each of these provide not only reviews of the state of the art project opinions on future efforts, but they also report on the numerous major milestones achieved by the ISP in the last few years. These milestones include the major expansions or completions of the European EEG Database at Freiburg and full launch of the IEEG-portal and database at the University of Pennsylvania. The cost of acquiring high quality, especially human, data, the need to use common data sets to adequately compare algorithm performance, as well as the inherent need for *long* recordings to account for statistical variability, vigilance state, drug tapering, etc., were early on identified as critical requirements by the ISPG.

In addition, the time between IWSP5 and IWSP6 was marked by major technological milestones. These include the first report on recordings and performance in humans of the NeuroVista recording and seizure advisory system (Cook et al. 2013). Long term is defined here as 6–18 months of continuous recordings in normally-active subjects. This effort not only produced evidence that seizure forecasting was achievable, but it produced a new level of never-before-seen detail in long-term brain activity recordings. In addition, this time period marked the FDA approval of the NeuroPace Responsive Neural Stimulation systems. These, in addition to emerging technologies that have the potential to develop into the next generation of implantable devices for the detection, prediction, and control of epileptic seizures, are reviewed by (Nagaraj et al. 2015).

Conclusion

We end this editorial with three notes: First, a statement of success: The road to successful seizure prediction and control is fraught with challenges. As evidenced above, we are making steady progress. Second, a note of caution: It is our concerted opinion that progress will continue to be a merger between technology, clinical and basic science insight. And finally, two notes of thanks. It has been an honor to have organized this meeting and been part of this community. In addition, our co-organizer Susan Arthurs, Chair of the Alliance for Epilepsy Research provides the amended note from the patient's perspective.

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