INVITED REVIEW

Seizure Detection, Prediction, and Forecasting

Aradia Fu and Fred A. Lado

Department of Neurology, Zucker School of Medicine at Hofstra-Northwell, Great Neck, New York, U.S.A.

Summary: Among the many fears associated with seizures, patients with epilepsy are greatly frustrated and distressed over seizure's apparent unpredictable occurrence. However, increasing evidence have emerged over the years to support that seizure occurrence is not a random phenomenon as previously presumed; it has a cyclic rhythm that oscillates over multiple timescales. The pattern in rises and falls of seizure rate that varies over 24 hours, weeks, months, and years has become a target for the development of innovative devices that intend to detect, predict, and forecast seizures. This article will review the different tools and devices available or that have been previously studied for seizure detection, prediction, and forecasting, as well as the associated challenges and limitations with the utilization of these devices. Although there is strong evidence for rhythmicity in seizure occurrence, very little is known about the mechanism behind this oscillation. This article concludes with early insights into the regulations that may potentially drive this cyclical variability and future directions.

Key Words: Seizure, Detection, Prediction, Forecasting.

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The unpredictability of seizures causes a great amount of distress and disruption to life in people with epilepsy. With the advent of digital EEG and inexpensive computers, there has been increasing interest in the development of seizure-detection and seizure-prediction devices to aide in the management of epilepsy. The first publication on seizure prediction appeared in 1975 and used scalp EEG to predict.[1] With emergence of the theory of nonlinear systems in the 1980s, researchers in the 1990s analyzed both scalp and intracranial EEG using complex nonlinear dynamics to predict seizures rather than using the conventional linear system.[2] The promise of these approaches led to the First International Collaborative Workshop on Seizure Prediction held in Bonn, Germany, in April of 2002. However, this early excitement was soon followed by growing skepticism regarding earlier reports of seizure prediction. An influential review published in 2007 challenged the feasibility of clinical applications based on seizure prediction.[2] Despite doubts, significant advances in the field of seizure prediction continued, including the first prospective trial in man in 2013 that demonstrated that long-term seizure prediction is possible based on electrocorticography recorded by an implanted device.[3] Today, the field of seizure detection and prediction is gaining momentum because of an improved understanding of ictogenesis and seizure-prediction algorithms and increasing amount of data from implantable devices. In this review, we assess the state of the field and utility of available devices to detect, predict, and forecast seizures.

WHY DO WE NEED SEIZURE DETECTION AND PREDICTION

One of the most disabling aspects of epilepsy is the unpredictable occurrence of seizures, which may cause serious injuries to individuals. Bilateral tonic–clonic seizures are associated with the highest morbidity and mortality. On average, 25% of individuals experiencing bilateral tonic–clonic seizures will sustain at least one serious seizure-related injury annually.[4] Among people with epilepsy, risk of sudden unexpected death in epilepsy is approximately one per 1,000 person-years. This risk is greatest in individuals with poorly controlled seizures and greatest in those having recurrent bilateral tonic–clonic seizures. A nation-wide population-based case–control study concluded that generalized tonic–clonic seizures during the preceding year were associated with 27-fold increased risk of sudden unexpected death in epilepsy. Among this cohort, sleeping alone increased the risk of sudden unexpected death in epilepsy to 67-fold.[5] Uncontrolled seizures also negatively impact individuals through social stigma, limiting individuals' day-to-day activities (e.g., no driving), contributing to low employment and increased dependency. Reliable detection and predication of seizures—i.e.,-identifying days of high-seizure risk—would improve individuals' quality of life and assist clinicians in clinical decision making to optimize the management of epilepsy. Accurate seizure prediction and detection coupled with implanted devices also offer possibility of seizure prevention in advance or at the time of seizure onset.

SEIZURE DETECTION VERSUS PREDICTION VERSUS FORECASTING

Seizure "detection" refers to the recognition of a seizure clinically, for example, by accelerometer on the body or electrographically by EEG. Seizure-detection algorithms largely focus on early recognition of electrographic seizure onset, which may occur a few seconds before clinical onset. Implicit in this analysis is the assumption that the seizure development in EEG follows a deterministic path, with the interictal EEG state transitioning to a preictal state and ultimately to an ictal state. In a closed-loop system, where seizure detection is coupled with seizure treatment, for example, by electrical stimulation of brain to terminate seizures, early seizure detection may increase the

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Address correspondence and reprint requests to Fred A. Lado, MD, PhD, Department of Neurology, Zucker School of Medicine at Hofstra-Northwell, 611 Northern Blvd #150, Great Neck, NY 11021, U.S.A.; e-mail: flado@northwell.edu.

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probability of aborting the seizure. Even in the absence of intervention, early seizure prediction still serves to alert an individual or care provider that a clinical seizure is imminent. Conversely, seizure-prediction algorithms analyze the preictal EEG in advance of electrographic seizure onset, to determine when a future seizure will occur so that there is sufficient time to prevent seizures.[2] For example, prediction that a seizure will occur in a few minutes may give sufficient time to use an inhaled benzodiazepine to prevent the seizure. This deterministic nature of seizure prediction (i.e., "a seizure will occur in 3 minutes") may be distinguished from the probabilistic nature of seizure forecast (i.e., "there is a 50% chance a seizure will occur in the next 12 hours"). Although seizures appear sporadic and unpredictable in their occurrences, large chronic EEG data sets suggest that seizures are organized in cyclic patterns with circadian (day–night), multidien (multiday), and circannual (yearly) variations.[6] Therefore, seizure-forecast algorithms aim to assess the probability of seizure occurrence in a particular time frame rather than the precise time of next seizure occurrence. Identifying features of circadian and multidian seizure risk based on features in the EEG showing circadian or multidian variability—for example, changes in the frequency of interictal epileptiform discharges, or changes in the spectral properties or cross-correlation between locations recorded in the EEG signal—may allow prediction of those periods when there is a greater statistical risk of seizures.[7]

Development of prediction and forecasting algorithms must overcome numerous challenges inherent to samples of biometric signal—such as EEG or ECG—and algorithm development. Predictions or forecasts of seizures from EEG signals may be affected by the state of vigilance or levels of antiseizure medications, and a relative paucity of long-term EEG recordings that may each confound seizure prediction.[6,8] What is needed are long-term EEG data sets from individuals in their usual environment. Adding information, for example, about circadian rhythms and vigilance state improves algorithm performance.[9] Algorithm development is also hindered by heterogeneous outcome measures—such as time horizon and specificity of the prediction—that complicate comparison of algorithm performance. Although still incomplete, over the past decade, there has been greater effort to standardize measures of prediction performance. Even so, a recent review found that seven of 12 studies reported preictal changes 13 minutes or more before seizure onset, up to an hour in some cases.[10]

The small sample size of seizure recording in publicly available databases has also been a hindrance to the development of statistically robust algorithms for seizure prediction or forecasting. Freestone et al.,[11] as well as others, have observed that because, of necessity, sample EEG data sets are relatively small, few of algorithms published prospectively tested prediction algorithms or used statistically appropriate controls. These investigators went on to identify additional shortfalls of seizure prediction algorithms inherent to the development of these data sets using recording of individuals in epilepsy monitoring units. As data sets contain only a few seizures for each individual, algorithm development requires pooling of data across individuals and potentially across different seizure types or circuits, thereby losing unique features that might be useful in individuals or for particular seizure subtypes. Because the number of individuals and seizure mechanisms are larger and even more heterogeneous than the test group used in algorithm development, prediction algorithms may work less well. The conditions of the inpatient unit also differ from seizure collected in the "normal" state. Antiseizure medications are often reduced during monitoring, and circadian routines are altered.

Open-source repositories of long-term scalp and intracranial recordings have been a valuable innovation in the development of seizure prediction and forecasting tools, providing standardized data sets that allowed comparison of performance of different algorithms. However, as noted, the small size of these open databases was also a limitation on the advances possible. The Freiburg data repository, for example, contained intracranial EEG (ICEEG) recordings for 21 individuals with drug-resistant focal epilepsy. Seizure prediction with 100% accuracy and low false-positive detections were reported for algorithms trained on this data set.[7] However, it has been observed that even long-term recordings contained in the Freiburg repository contain only a few seizures per individual and data recording durations comprise days, rather than weeks or months. With a relatively small number of individuals, seizures, and recordings days, there is a risk of overtraining algorithms to recognize the recorded seizures in the small data set—so called over-fitting, only to see the algorithm perform poorly when faced with novel seizure recordings. Indeed, algorithms developed on long-term EEG recording with dozens or hundreds of seizures per subject have performed with accuracies substantially lower than those reported with the Freiburg data set.[7]

Size of EEG data sets has been a key limitation for the development and testing of seizure prediction and forecasting tools. For many individuals living at home, seizures may occur once or twice monthly or even less frequently. Yet EEG data sets are largely drawn from hospitalized individuals in epilepsy monitoring units where antiseizure medications have been reduced to increased likelihood of recording a seizure, and recording duration is only a few days. Changes in seizure medication levels and sleep patterns or other circadian rhythms may each result in EEG changes that confound prediction and forecasting algorithms. The Freiburg data set has been superseded by more extensive data sets such as the European Epilepsy Database (http://epilepsy-database.eu/) that is in development; currently, it offers scalp and ICEEG recordings from 60 individuals, with future plans to offer recordings from more than 200 individuals, comprising more than 2,500 seizures and more than 45,000 hours of EEG recording. It remains to be seen if the data collected in this data set sufficiently reflect the conditions of regular life lived by individuals with epilepsy to advance prediction and forecasting.

On the horizon are implantable and wearable devices that promise prolonged recordings at the cost of reduced number of recording channels. The development of chronic subcutaneous recording devices—along with existing intracranial responsive neurostimulation (RNS) devices able to record EEG—promises access to individualized data collected over a period of months or years.[11,12] Deep learning algorithms that detect and learn features relevant in each individual without prior knowledge of patterns would allow training of algorithms customized to each individual.[11–13] Results from competitions between the teams to develop

the most robust seizure prediction using standardized data sets indicate that the most successful approaches use a multitude of pattern detectors. The combination of detectors that are most informative will differ from individual to individual, so using multiple detectors increases the likelihood of success.[14,15]

EEG-Based Prediction and Forecasting Algorithms

EEG-based algorithms use features of the EEG to assess the likelihood of seizure in a determined time horizon. Features may be extracted from the time series data or from the frequency spectra or phase-space features, the latter being measure of dynamical properties embedded in the EEG signal. Time-domain features of EEG include amplitude, variability, and regularity of individual channel time series and measures of synchronicity between EEG channels. Frequency-domain analysis examines the changes in spectral content of EEG signals over time—often with wavelet analysis—to identify patterns associated with increased seizure likelihood. Most investigators use the pattern of time- or frequency-domain features to infer the likelihood of seizure, i.e., inferring interictal versus preictal brain states—from EEG signals alone. Some investigators have inverted this approach beginning with a computational model of critical neural circuits, such as hippocampus or neocortex, to predict expected EEG features and then used presence or absence of these features to classify an individual EEG as interictal or preictal.[10] Niknazar et al.[16] have performed a survey of a wide number of EEG features used for seizure detection. These investigators reported that phase space algorithms that identify the pattern of evolution of seizure discharges performed best in detecting seizures.

A proof of concept validating the feasibility of seizure prediction in humans was conducted in the NeuroVista study.[3] Fifteen individuals received a standardized electrode implant to record and transmit ICEEG to a handheld receiver. Eleven individuals continued to the next phase of the study where seizures were recorded so that prediction algorithms could be adjusted and customized for the individual. Nine individuals entered the final phase of the study, testing the accuracy of the individualized prediction algorithms over the course of four months. Prospective prediction accuracy was better than chance in all nine individuals. Three individuals had high seizure-prediction sensitivity. Sensitivity was 86% in one individual who experienced 13 seizures in the observation period. Sensitivity was 100% in two individuals who experienced three seizures each in the observation period. Time spent under warning of high seizure likelihood was 27%, 31%, and 3%, respectively. In the other six individuals who entered the final phase of the study, sensitivities ranged from 54% to 71%, and time spent under warning of high seizure likelihood was 15% to 41%.[3,14]

Non–EEG-Based Seizure Prediction and Forecasting Algorithms

Compared with EEG-based prediction and forecasting, relatively little work has been done predicting seizures independently of EEG measures. The advent of wearable devices, including motion and biometric recorders, may open additional sources of data that may contribute to seizure prediction. One readily available source of data is the individual themselves. Cousyn et al., used a review of the literature to identify the most common reported prodromal symptoms. Typical prodromal symptoms included, for example, trouble concentrating, reading, speaking, or writing, noise or light sensitivity, irritability, or poor mood, to name only a few. During inpatient evaluation averaging 10 days, subject competed a daily survey of 24 symptoms, rating each with a 4-level Likert scale ranging from "not at all" to "very much so." Surveys were sorted into preictal days, where a seizure occurred within 24 hours of the survey, or interictal days where no seizure occurred within 24 hours. Prediction algorithms were trained on 70% of the days recorded and then tested on the remaining 30% of days. Linear regression techniques were inferior to machine learning "support vector machine" algorithms, with the latter method able to predict seizures with 70% accuracy (sensitivity 72%, specificity 68%) with only structured reporting of subjective state by individuals. As with many EEG-based studies, these investigators acknowledge that the use of inpatient reports, with only a short period of observation available, was a limitation of the study. What is more, subjects had on average 3.8 seizures during the evaluation, an insufficient number to optimize the prediction algorithm to each individual.[17]

Taking into consideration the environmental factors, such as sleep, weather, and temporal features such as time of day or time of year, may also independently improve seizure forecasting. Payne and colleagues examined the occurrence of seizures in eight individuals in relation to these variables using long-term recordings acquired over months in the NeuroVista study. Although these subjects participated in the NeuroVista study, intracranial EEG was used as a gold standard for seizure occurrence, but EEG-based algorithms were not part of the prediction analysis. Payne et al.,[18] found that seizure could be predicted above chance by examining duration of sleep in five individuals, weather cycles in two individuals, and temporal features in six individuals, and combining features improved performance in a substantial proportion of individuals.

Vandecasteele et al.,[19] compared the sensitivity of seizure detection algorithms applied to three different standardized data sets of intracranial EEG with and without inclusion of ECG signals and found that inclusion of ECG increased detection sensitivity to 8% and 11% in two of three seizure data sets examined. Analysis of long-term recording of heart rate measured using wearable technology has similarly been found to help forecast periods of increased seizure risk.[20] Karoly et al., examined heart rate data recorded using smartwatch technology and correlated changes in heart rate with seizure diary data. Investigators compared 31 individuals with uncontrolled epilepsy and 15 healthy controls. Average duration of recordings was 12 months, with SD of 5.9 months. Individuals in the seizure group averaged 72.4 seizures during observation with a wide range in seizures counted (0–416 seizures). Nineteen individuals had 20 or more seizures during the observation period, allowing statistical correlation with circadian variations in heart rate. Heart rate variations were present in all participants in both groups, whereas weekly cycles and monthly cycles were present in 25 of 46 and 13 of 46, respectively. In 19 individuals with enough seizures to analyze, 17 (89%) had seizures that were more likely to occur locked to at least one heart rate cycle. Fourteen were locked to a circadian cycle, 10 were locked to multiday cycles,

and eight showed influence of both circadian and multidian cycles. Merging data streams from long-term seizure diaries or recordings of biometric data including sleep, temperature, and activity, environmental data, and finally either scalp or intracranial data hold significant promise in improving seizure forecasting to a level that will be clinically useful to people with epilepsy. The explosion in wearable technologies, discussed later in the text, offers a growing number of data sources with the potential to better distinguish days of increased seizure risk from days of low risk.[21]

DEVICES AVAILABLE AND THEIR USE FOR SEIZURE DETECTION, PREDICTION, AND FORECASTING

Hospital-Based Devices

Both surface and intracranial recordings data have been studied for seizure prediction, although most studies favor intracranial recording because of higher signal-to-noise ratio, better spatial resolution, minimal artifacts, and potential to record directly from the seizure-onset zone.[2]

Noninvasive Ambulatory Devices

Self-Reported Seizure Diaries

To facilitate self-monitoring of seizures, seizure-related symptoms, and therapies, free web-based applications, such as My Epilepsy Diary (http://www.epilepsy.com/seizurediary) or Seizure Tracker (https://seizuretracker.com), provide cloud platforms where individuals may keep a seizure diary to share with their doctors to better guide individual treatment plans.[22] Several studies have demonstrated the utility of seizure diaries and other self-monitoring exercises in seizure prediction and forecasting.[23–25]

Noninvasive Devices

With technology advancements and increasing awareness and interest in personalized health, there has been a surge in mobile and wearable devices,[26] including products to detect and predict seizures. Wrist-worn accelerometers with predetermined algorithms and thresholds have robust evidence for the detection of generalized tonic–clonic seizures.[27] Bed alarms comprised movement sensors under the mattress that have proven useful in detecting nocturnal motor seizures.[28] Surface electromyography alerts seizures by detecting seizure-related muscle activity and distinguishing it from physiological muscle activation.[29] Automated video analysis has also proven sensitive in detecting generalized tonic–clonic seizures.[30] Combining multimodal measurements that employ a combination of sensors to detect changes in biosignals like heart rate, oxygen saturation, respiratory, and galvanic skin responses with the use of accelerometers hold promise in increasing likelihood of noninvasive seizure detection.[31,32]

Implantable Ambulatory Devices

Vagal Nerve Stimulation

Vagal nerve stimulation involves the use of an implanted pacemaker-like device that is programmed to intermittently stimulate the left vagus nerve with electrical impulses through two electrodes.[33–36] The device was first approved in the EU in 1994 without the ability for seizure detection. Then, in 2014, a responsive vagal nerve stimulation device was introduced into the market that delivers automated stimulation in response to rapid heart rate, a prevalent symptom at seizure onset. This closed-loop design of vagal nerve stimulation enables the device for potential use in detecting seizures and improves its therapeutic value for the treatment of epilepsy.[37]

Subcutaneous and Subgaleal EEG

There has long been a need for long-term ambulatory EEG where seizures may be recorded and accurately quantified in individuals' day-to-day milieu. 24/7 EEG SubQ produced by UNEEG Medical in Denmark is a novel portable EEG acquisition system that is composed of three subcutaneously implanted leads and an external logging device. Only local anesthesia is required for the implantation. The device can record for approximately three months, "ultra-long-term monitoring," to distinguish it from "long-term monitoring," where typical durations are less than one month. Nine participants with temporal lobe epilepsy were implanted with a beta-version of the 24/7 EEG SubQ in this subcutaneous EEG trial with three months of continuous home monitoring of seizures without any restrictions on activities. This first study demonstrating that real-life ultra-long-term monitoring with subcutaneous EEG is feasible, safe, and well tolerated, has increased optimism for a new era of home-based monitoring.[38] Similar to subcutaneous EEG, there have been studies exploring the use of subgaleal EEG for long-term seizure monitoring.[39,40] Subgaleal EEG recording demonstrates similar signal characteristics to scalp and subcutaneous EEG recordings, with the notable difference in that SG recordings, given their uniquely positioned electrodes, are less affected by artifacts from muscle activity in the face, jaw, and neck or by motion.[40] Pacia et al., reported reliability of single-channel subgaleal EEG in identifying focal and secondarily generalized seizures that was validated by simultaneous ICEEG recording. A single, six-contact, subdural strip was implanted at or near the cranial vertex in 21 epilepsy patients who were at the same time undergoing ICEEG for up to 13 days. Three EEG experts blinded to the ICEEG reviewed 219 samples of 10-minute subgaleal EEG recordings with 81 seizures of temporal, extratemporal, or simultaneous temporal/extratemporal onsets. Study showed that readers correctly identified 98% of temporal and extratemporal onsets that were validated by ICEEG recording, with 98% sensitivity and 99% specificity.[40] Subcutaneous and subgaleal EEGs thus far have been used as tools for seizure detection, but their ability to collect long-term recording make them valuable for potential seizure forecasting.

Responsive Neurostimulator

The RNS system is the first responsive (closed-loop) therapeutic device that is cranially implanted with two four-contact intracranial electrodes that continuously monitor and record cerebral electric activity from or near the epileptogenic focus/foci. The device may be programmed to recognize seizure patterns unique to the person and, upon detection of such patterns, to deliver electrical stimulation aimed at aborting an

incipient seizure. The RNS system also allows for long-term intracranial recording of interictal epileptiform activity and electrographic seizures.[41] In multiple clinical trials of the NeuroPace RNS System, 256 participants with drug-resistant focal epilepsy have been implanted with the RNS system, and 12 years of intracranial data have been collected and analyzed. In these recordings, there are both circadian and multidian oscillations in interictal activity. Seizures tend to occur at particular phases of these rhythmic cycles.[42,43] This observation raises the possibility that it may be feasible to use RNS data to forecast in advance days with greater probability of seizure occurrence.

Canine Data (Chronic ICEEG)

Seizure forecasting devices with ICEEG recording have been tested using canine epilepsy model. One study implanted an ICEEG recording system with four 4-contact strips that recorded and wirelessly relayed data to an external advisory device placed in a harness on the dog's back. The advisory device signaled seizure detection or prediction through visible or audible alarms and through email and text messages. Three dogs with naturally occurring focal epilepsy were implanted, and intracranial data were collected over 15 months. The study found a seizure forecasting algorithm performed significantly better than chance predictor, suggesting that seizures occurrence was not random, supporting the feasibility of seizure forecasting.[44] Other studies have replicated similar findings.[45,46]

NeuroVista

The results from the NeuroVista trial are discussed in a prior section. The NeuroVista device was a noncommercialized seizure advisory system manufactured by NeuroVista Corporation, Seattle, WA, that is no longer in operation. The advisory system consisted of two electrode arrays with 16-contacts implanted over the cortical surface presumed to be the epileptogenic zone and a telemetry unit implanted under the clavicle, sampling 16 channels of EEG. The telemetry unit wirelessly transmitted to a portable handheld advisory device that displayed visual and auditory signals indicating the likelihood of a seizure in the next few minutes or hours. The advisory device was also capable of storing EEG recording. NeuroVista trial enrolled 15 participants with drug-resistant focal epilepsy. The study concluded that the device predicted seizures with 65% to 100% sensitivity.[3] Participants wore the device for up to two years, and the long-term intracranial data were also used to forecast seizures, confirming the presence of circadian pattern to seizures.[47] Further analysis of the data set also revealed that interictal epileptiform activity also fall under a circadian regulation and that the probability distribution of interictal activity and seizures were quite similar, suggesting that the two phenomena may not be independent.[48]

Challenges and Limitations

In recent years, there have been increasing commercialized popularity among individuals and media for the use of non–EEG-based seizure detection mobile and wearable devices. However, despite enthusiasm in the nonscientific community, the use of devices by clinicians has not gathered equivalent momentum because of the lack of diagnostic accuracy. Seizure detection using mobile and wearable devices has the best evidence for generalized tonic–clonic seizures (highest sensitivity and lowest false alarm rate), limited evidence for other motor seizures, and scarce evidence for nonmotor seizures.[49]

It is well-established that individuals and caregivers are unreliable in reporting seizure frequency, often underreporting because of unawareness of seizures[50]; the need for automated ambulatory seizure detection is evident. There is strong evidence for the validity of EEG-based seizure detection,[49] but individuals do not like the visibility of scalp electrodes, and implantable intracranial devices are invasive and often require extensive workup to determine precise placement of the electrodes. Minimally invasive ultra-long-term subcutaneous recording may launch a new era in ambulatory monitoring, but it is not without disadvantages such as reduced spatial resolution compared with standard scalp-EEG.[51] Future trials and investigations are in need to further explore and establish the clinical utility of subscalp EEG. Cyclic patterns of seizures concluded from chronic EEG data sets from NeuroPace RNS System, NeuroVista, and subcutaneous EEG trials were based on participants with focal epilepsy. It is unclear whether generalized epilepsy will manifest similar cyclic variations. There are intricately intertwined and complex dynamics between external seizure precipitants and internal regulators of seizure cycles. Behavioral and environmental precipitants, such as alcohol and weather, may arise to influence or disrupt the endogenous mechanisms driving the rhythmicity of seizures, promising further challenges to reliably forecast seizures outside of controlled studies.[52]

CONCLUSIONS

The seemingly random occurrence of seizures is often the cause of fear and uncertainty in individuals with epilepsy. The ability to reliably predict and forecast seizures would bring about a monumental change in the management and treatment of epilepsy. There have been many advances in this seizure prediction over the past decade, but larger data sets from chronic EEG recordings are needed to gain further insights into the circadian and multidien cycles of seizure. These insights will be critical in constructing clinically applicable algorithms for seizure prediction and forecast. Additional innovation is needed to develop devices that are (1) minimally invasive or noninvasive, (2) well concealed and comfortable, and (3) cost-effective.

There is now solid evidence for the presence of rhythmicity in the multiple time scales in seizure occurrence, but the mechanism underlying such rhythmicity remains unclear. Many physiological events exhibit cyclic behavior with peaks and troughs, modulated by intrinsic pacemakers. Some of the best-studied examples include hormonal regulations of menstrual and sleep–wake cycles. Increasing studies in the last few years have proposed possible molecular oscillators underlying the circadian and multidien variations in epilepsy.[53–56] The proposed concept is that there are oscillations in genes that respond to external stimuli, like light or food, leading to circadian variation in protein expression, as well as those that respond to internal stimuli that result in slower multidien variation in protein expression.

Cascade of changes to the molecular and cellular pathways then follows as the downstream effect of rhythmicity in protein expression, leading to the regulation of the multitemporal cycles of seizure activity. Future studies are needed to further explore this revolutionary framework that opens door to novel biomarkers and potential precision medicine in epilepsy.

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