Epilepsy Research (2011) **97**, 243—251

journal homepage: www.elsevier.com/locate/epilepsyres

What is the present-day EEG evidence for a preictal state?

William Stacey[a,b], **Michel Le Van Quyen**[c], **Florian Mormann**[d], **Andreas Schulze-Bonhage**[e,*]

[a] *Dept. of Neurology, University of Michigan, USA*
[b] *Dept. of Biomedical Engineering, University of Michigan, USA*
[c] *Centre de Recherche de l'Institut du Cerveau et de la Moelle épinière (CRICM), INSERM UMRS 975 — CNRS UMR 7225 — UPMC Paris 6, Hôpital de la Pitié-Salpêtrière, Paris, France*
[d] *Dept. of Epileptology, University of Bonn, Germany*
[e] *Epilepsy Center, University Hospital Freiburg, Germany*

Received 14 February 2011; received in revised form 4 July 2011; accepted 27 July 2011
Available online 31 August 2011

KEYWORDS
Seizure prediction;
EEG;
Recording techniques;
Frequency spectrum;
High frequency oscillations;
Statistical evaluation

Summary EEG-based seizure prediction has undergone phases of optimism when analyses based on limited EEG samples suggested high sensitivity and specificity for several algorithms extracting features from raw preictal EEG data. When using long-term recordings, a more realistic view emerged which suggests that statistically significant predictions might be possible from surface and intracranial EEG, but no algorithm has yet demonstrated performance allowing for clinical application. Here, progress in EEG recording techniques, EEG analysis, and requirements for proper statistical validation of results are reported and discussed as they pertain to clinical implementation.

Introduction

Millions of people worldwide suffer from intractable epilepsy. The sporadic and often dangerous nature of seizures greatly reduces patients' quality of life. There is much interest in developing automated algorithms for seizure detection to automate clinical diagnostic procedures, and hope that new, preemptive therapies might be possible if seizures could be predicted before they begin. As computational power matured over the last 40 years, many researchers investigated putative seizure precursors within patients' electroencephalograms (EEGs). Early studies, which were preliminary descriptions of possible techniques, later led to small trials that had promising results. However, later analyses could not reproduce these optimistic findings in a prospective, statistical fashion (for review see Mormann et al., 2007). One key finding, however, was that many patients have electrographic changes prior to seizures (Mormann et al., 2005): statistical evidence of a ''preictal state'' that could be used for therapeutic decisions if suitable algorithms can be developed to detect it

* Corresponding author.
E-mail address: schulzeb@nz.ukl.uni-freiburg.de (A. Schulze-Bonhage).

0920-1211/$ — see front matter © 2011 Elsevier B.V. All rights reserved.
doi:10.1016/j.eplepsyres.2011.07.012

prospectively. To be valid, these seizure prediction algorithms must demonstrate that they perform better than chance in a prospective fashion (Snyder et al., 2008). Unfortunately, to date there are no published results that have succeeded. Presently, research groups in the field of seizure prediction are active in several fronts: selection of the best signal for prediction using technological advances in digital EEG, improvement of analysis techniques, and application of adequate performance analyses. The following sections provide a perspective on the state of seizure prediction in light of new advances in electrode development, signal acquisition, data processing, computational analysis, and statistical evaluation.

Improving seizure detection and prediction: a bioengineering perspective

Ongoing technological advances in digital EEG and successes of implantable electronics to control seizures (Stacey and Litt, 2008) have fostered interest in developing methods to detect seizures or predict them before they become clinically manifest. Success in the endeavor to develop clinical seizure prediction applications will depend upon utilizing a combination of clinical and engineering expertise to overcome several important challenges.

Most current EEG standards were built around early 20th century technology. With the advent of digital sampling, many of these limitations are no longer present. Data can now be analyzed automatically to generate quantitative measures of EEG signals, and ''quantitative EEG'' is already available in many commercial systems. Several commercial companies now offer intracranial electrode grids that contain ''microelectrodes'' with high spatial resolution. Digital sampling can easily overcome the early limitations of pen-and-ink machines that could not draw faster than 70 Hz, and can now be used to monitor for much higher frequencies. These breakthroughs have led to a new age in EEG.

Among the first endeavors with digital EEG were attempts to develop seizure detection algorithms. These algorithms try to recognize specific patterns that represent seizure activity in real time, and produce a mark on the EEG to alert the clinician of a seizure. In practice, however, these algorithms can be unreliable and cannot substitute for human review. Perhaps this is not surprising, since some seizures are notoriously difficult to identify, and human reviewers often disagree (Abend et al., 2011; Benbadis et al., 2009). Several other groups have investigated methods to predict seizures before they occur, utilizing various mathematical algorithms to evaluate changing EEG trends (Lehnertz and Litt, 2005; Maiwald et al., 2004; Mormann et al., 2007). After analyzing many different methods for seizure prediction, Mormann et al. determined that while there was potential for success, no method had yet been able to predict seizures reliably (Mormann et al., 2005). After over 10 years of research, reliable methods to detect and predict seizures remain elusive.

There are two schools of thought regarding how to develop successful algorithms for seizure detection and prediction. The first is to develop better ways of analyzing the available data, processing them with powerful computational clusters to develop new algorithms based on different quantitative features. This approach, which is currently in use by several commercial companies, makes use of specialized feature extraction and data mining for both seizure detection and prediction. These improvements are continually refined and generally lead to proprietary algorithms. Detection algorithms are trained on marked datasets, while prediction schemes required development of a unique system that utilizes statistics to compare an algorithm with random chance (Mormann et al., 2007; Snyder et al., 2008) (see later section). Another important development is the formation of shared, international seizure databases, which make annotated EEG available to researchers around the world and provide well-organized data for both training and testing of algorithms. These databases provide sufficiently long continuous data sets to avoid overfitting of algorithms, allow for adequate statistical evaluation and use of separate training and test datasets for evaluation of prediction algorithms (Ihle et al., 2010).

The second school of thought is that many of the challenges in seizure detection and prediction are because conventional EEG data is insufficient for the task. Several groups are recording EEG with higher spatial and/or temporal resolution, and find that high frequency oscillations (HFOs) have a strong relationship with the seizure onset zone (Crepon et al., 2010; Jirsch et al., 2006; Schevon et al., 2009; Worrell et al., 2004, 2008). HFOs can reach 600 Hz and are filtered out of conventional EEG, so decades of EEG teaching and research have not accounted for this activity. Analysis of intracranial EEG with higher sampling rates demonstrates that HFOs are visible if the cutoff frequency is high enough (Fig. 1A). As described in the next section, the clinical significance of HFOs is still under investigation, as researchers attempt to clarify the relationship between HFOs and seizure activity, searching for new electrophysiological biomarkers of epilepsy (Engel et al., 2009; Le Van Quyen et al., 2006). This research highlights the advantage of engaging new technology into epilepsy research. There are several new technologies currently under development that seek to expand our knowledge of epilepsy even further.

Improved electrodes: The standard size and spacing of intracranial electrodes for clinical epilepsy and electrocorticography has not changed in 50 years. The HFO studies mentioned above depended upon increased sampling frequency and, in some cases, improved spatial resolution. The ideal size and sampling rate for intracranial electrodes is still unknown and is an active area of investigation. Different filter bandwidths alter the data that is visible to clinicians, and studies are underway to determine how they will affect clinical decision-making (Fig. 1). One intriguing new phenomenon, ''microseizures'' that are visible only on single microelectrodes, suggests that higher spatial resolution may yield important new data about seizure mechanisms (Schevon et al., 2008, 2009, 2010; Stead et al., 2010; Worrell et al., 2008). Further improvements in resolution and wiring are now possible using advanced photolithographic techniques for electrodes with flexible silicon electronics (Viventi et al., 2010) or bioresorbable silk backing (Kim et al., 2010) (Fig. 1D). These technologies strive to record from many cortical regions simultaneously, down to the level of cortical columns or even clusters of individual neurons. This ambitious endeavor will bridge the gap between large scale clinical recordings (EEG) and the wealth of ongoing

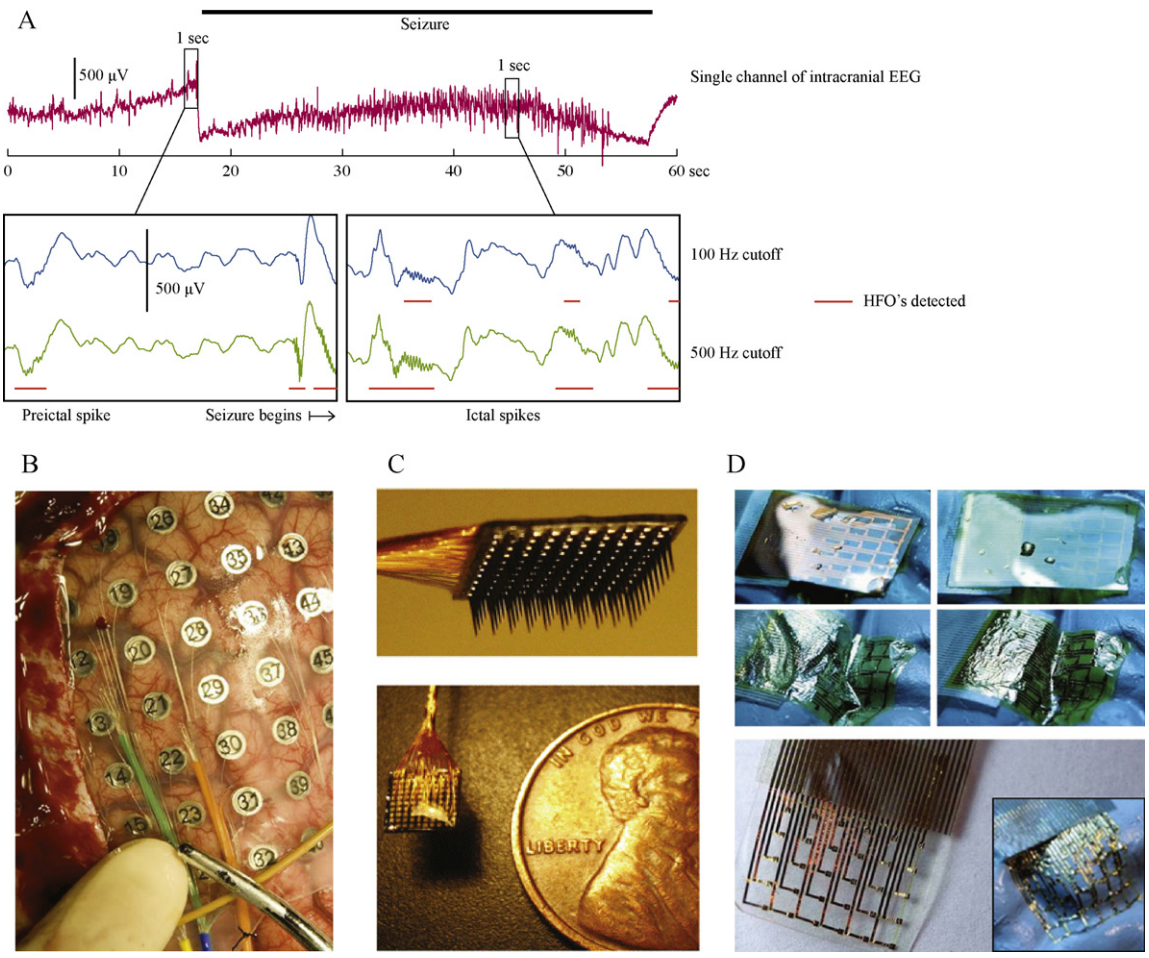

Figure 1 Improved temporal and spatial EEG sampling: (A) Human intracranial EEG before and during a seizure was sampled at 32 kHz, downsampled to 2713 Hz, then filtered with either a 100 or 500 Hz high frequency cutoff. HFOs are visible preictally only with the 500 Hz cutoff, and are also much more prominent during the seizure (from Ritaccio et al., 2010, with permission). (B) Standard intracortical grids (numbered) are bisected by two clusters of microelectrodes in orange and green wire bundles (from P. House, University of Utah Dept. of Neurosurgery, with permission). (C) The ''Utah array,'' with 100 penetrating microelectrodes in a 4 mm square grid (from Kelly et al., 2007, with permission). (D) Thin, flexible arrays can sample from high spatial resolution and conform well to the brain surface (top). Silk-backed arrays have similar resolution, better conforming properties, and are bioresorbable (bottom) (from Kim et al., 2010, with permission).

translational research at the single-neuron level in epilepsy (Truccolo et al., 2011), normal brain function (Quiroga et al., 2005, 2008) and decoding for brain–computer interfaces (Ritaccio et al., 2010; Vargas-Irwin et al., 2010). These electrode arrays hold great potential to uncover crucial information about brain network behavior during both normal and seizure activity.

Automated algorithms: As spatial and temporal resolution increases, so does the amount of data processing needed. Intracranial EEG often contains over 100 channels that are read laboriously at 10 s per page (Crepon et al., 2010). It would not be feasible for clinicians to read hundreds of additional microelectrode channels, while simultaneously looking for low amplitude HFOs that last 100 ms each—the screen resolution alone does not allow for such an endeavor (Schevon et al., 2004). Furthermore, human readers are inconsistent in labeling HFOs (Gardner et al., 2007). Recent work demonstrates algorithms to automatically detect and classify HFOs within terabytes of human EEG data (Blanco et al., 2010; Dümpelmann et al., 2010). These algorithms provide a means to identify and evaluate large numbers of HFOs with strong statistical power to determine the relationship between HFOs and seizures.

Computational modeling: HFOs involve a fairly large network of cells oscillating at high frequencies, a spatiotemporal scale that is too fast and too large to characterize fully using current electrophysiologic techniques. Computational modeling is capable of predicting the type of network pathologies necessary to produce HFOs, as well as specific features that might help distinguish normal from abnormal activity. A recent computer model of HFOs demonstrated that altering the synaptic activity and coupling within a cortical network can generate epileptic HFOs (Stacey et al., 2009), and spread them to neighboring cells (Stacey et al., 2011). These results suggest that epileptic HFOs have distinct behavior and features from those arising in normal tissue. In the future, these simulations will help guide development of seizure prediction and detection algorithms.

Thus, bioengineering techniques are steadily pushing the cutting edge of seizure detection and prediction forward by acquiring EEG with better spatial and temporal resolution, developing automated analysis of EEG data, and suggesting mechanisms that underlie epileptic pathology with computational models. These technologies are currently being used in many labs throughout the world to understand the neurophysiological basis behind epilepsy.

The role of high frequency oscillations: a neurophysiological perspective

One of the major limitations of developing seizure prediction algorithms is our limited understanding of the cellular and network activity that generates seizures. One intriguing phenomenon that appears to be strongly related to epilepsy is that of high frequency oscillations (Engel et al., 2009). While there are undoubtedly many other cellular and network activities involved in seizures, HFOs have been widely studied, are fairly well-characterized and thus are a very promising candidate for a seizure precursor. Experimental and human data have accumulated which strongly suggest that very localized HFOs far beyond the spectral frequency limits of traditional EEG (>40 Hz, e.g. hippocampal ripples 140—200 Hz or fast-ripples 250—500 Hz) are not only an electrical signature of focal epilepsy during seizure-free states (Bragin et al., 2002; Crepon et al., 2010; Le Van Quyen et al., 2006) but may also play a causal role in the initiation of seizures (Bragin et al., 2004; Jiruska et al., 2010; Traub et al., 2001). Among different subgroups of fast rhythms, oscillations in the gamma and fast gamma frequency range (40—120 Hz) are well known in intracranial EEG recordings of partial seizures in patients with temporal and extra-temporal epilepsy. The reported frequencies of this fast brain activity on intracranial EEG recordings varied and included 20—80 Hz (Alarcon et al., 1995), 40—120 Hz (Fisher et al., 1992), 60—100 Hz (Worrell et al., 2004), 70—90 Hz (Traub et al., 2001) and 80—110 Hz (Allen et al., 1992). Additionally, in neocortical epilepsy, fast gamma oscillations were also intermittently present throughout the interictal period and a significant increase in interictal gamma amplitudes was reported several minutes prior to onset of an epileptic seizure (Worrell et al., 2004), suggesting that these oscillations can be useful for identifying periods of increased predisposition to clinical seizures. However, there are only a few detailed studies on the role of high-frequency oscillations in the preictal state, and early results showing that HFOs increased in the preictal period (Worrell et al., 2004) have later been questioned with different recording paradigms (Jacobs et al., 2009).

Although potentially of great relevance to the study of preictal phenomena, research on HFOs has been slow, mostly for technological reasons: (1) most clinical EEG systems have sampling rates that are too low—often 200 Hz or lower—to detect these oscillations; (2) these oscillations may be generated in very localized cortical regions requiring invasive intracranial electrodes or microelectrodes; and (3) the detection of these events is difficult and requires automated signal processing techniques that are still under development. For this purpose, several analytic tools for the study of human fast oscillations have been developed (Dümpelmann et al., 2010; Blanco et al., 2010; Crepon et al., 2010; Le Van Quyen and Bragin, 2007).

Currently, many groups are investigating high-frequency gamma activities in long-term (typically 7—10 days), high density/high sampling rate (1 kHz) intracranial recordings of patients with refractory epilepsies. These IRB-approved, prolonged recordings allow sampling of the full spectrum of physiological states for an individual patient. As previously reported (Worrell et al., 2004), during the interictal states of neocortical epilepsies, strong and localized gamma oscillations can be found close to the seizure onset zone. An example of this is shown in Fig. 2 (Le Van Quyen, unpublished data, methods similar to those described in Le Van Quyen et al., 2010). HFOs were intermittently present throughout the interictal records, and often occurred asynchronously at different electrodes within epileptic networks (Fig. 2A). Furthermore, many neocortical seizures (around 30%) were preceded by a build-up of high-frequency power in the hours prior to seizures (Fig. 2B). Nevertheless, when analyzed over a long period of time (several days), the high-frequency power within the seizure onset zone was strongly modulated by behavioral changes and, in particular, was maximal during seizure-free slow-wave sleep (Fig. 2C, see also Bagshaw et al., 2009). A similar modulation was previously reported for normal gamma oscillations, also known to be strongly expressed during sleep (Le Van Quyen et al., 2010; Steriade et al., 1996) and considered as a sign of specific cortical information processing enabling the consolidation of recent memory representation (Sejnowski and Destexhe, 2000). Thus, fundamental similarities between sleep activations and preictal fluctuations of high-frequency oscillations exist. As suggested by others (Worrell et al., 2004), increased high frequency activity seen before the onset of some seizures may be the result of an aberration of the same physiological mechanisms underlying memory consolidation during slow wave sleep. Indeed, as reported in patients with frontal lobe seizures (Della Marca et al., 2007), preictal gamma oscillations appear to be more prominent during slow-wave sleep compared with wakefulness or rapid eye movement sleep. These pathological gamma oscillations may be driven in the epileptic cortex by transient paroxysmal neuronal depolarization, facilitated by the strong potential fluctuations which occur during the slow oscillation, an effect predicted by recent modeling studies of HFOs (Stacey et al., 2009). One hypothesis about the relationship between HFOs and epilepsy is that recurrent high-frequency oscillations over time could trigger an activity-dependent reinforcement pathway like long-term potentiation (LTP), known to occur during normal sleep (Diekelmann and Born, 2010), leading to a progressive consolidation of local epileptogenic circuits and an increased probability to have a seizure.

Ongoing research projects in several different labs aim to understand the generation of seizures by analyzing neurophysiological activity such as HFOs. HFOs may not be the only or best phenomenon for understanding epilepsy, and it is crucial that this research combine expertise in many disciplines: neurophysiology, computational modeling, clinical epileptology, data analysis, etc. This collaborative approach, making use of new technology and methods as they are developed, will be necessary to elucidate the physiological basis for the electrographic signals recorded before

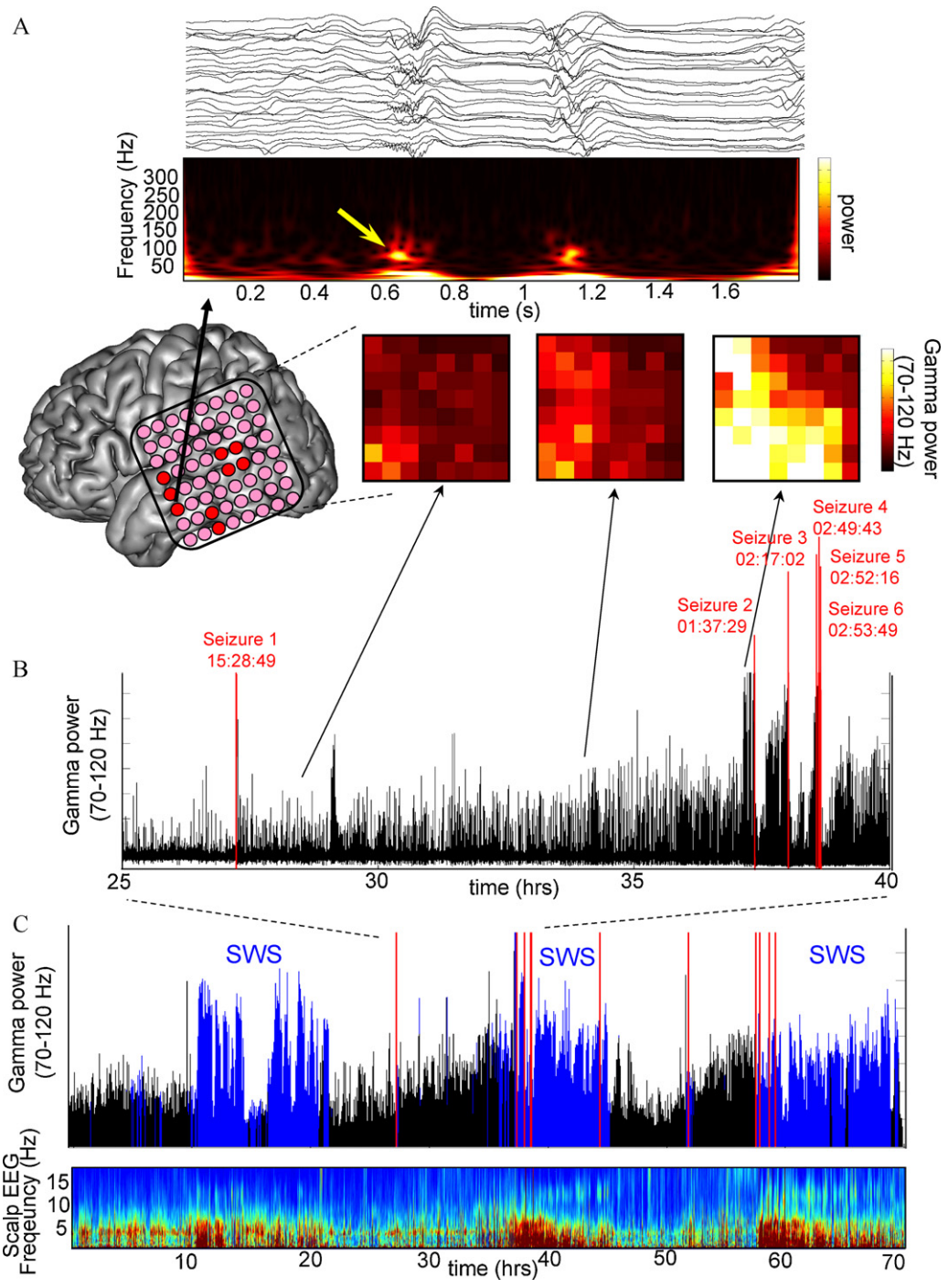

Figure 2 (A) Example of localized epileptic gamma oscillations in the seizure onset zone, recorded here with an intracranial subdural grid on a human patient undergoing evaluation for potential epilepsy surgery. The seizure onset zone is depicted with red circles on the reconstructed 3D MRI. Oscillations around 80 Hz (*yellow arrows*) were clearly distinguishable in the raw EEG or in the time-frequency map (*Bottom*). (B) Example of an increase of the high-frequency energy (here averaged over the seizure onset zone) seen hours before a seizure cluster (seizures from 2 to 6). This increase appears as a build-up in specific regions, as illustrated by the three consecutive spatial maps of gamma power in the grid (arrows). (C) With prolonged recordings (several days), it can be seen that high-frequency energy was strongly modulated by physiological changes, in particular during slow-wave sleep (SWS, blue). Sleep was independently identified by the slow components (<3 Hz) of the simultaneously recorded scalp EEG (*Bottom*).

and during seizures, potentially leading to a better understanding of how to detect and predict seizures.

Testing prediction algorithms: a statistical perspective

Advances in technology and neurophysiology are invaluable in developing seizure prediction algorithms, but it is crucial that these algorithms are evaluated correctly. Studies on seizure prediction can differ in many ways, e.g. whether they aim at detecting clinical or electrographical events, whether the goal is seizure prediction or an early detection of seizures, whether intracranial or scalp EEG is used, whether an algorithmic (prospective or quasi-prospective) or statistical (retrospective) evaluation scheme is used, how many and which EEG channels are used for prediction, whether continuous multi-day recordings or only short data snippets are used, whether the algorithm is based on detecting electrographical patterns and events or dynamical changes in the signal, etc. Furthermore, a number of confounding variables can influence the methods used to characterize EEG changes. Among these influences are circadian rhythms, AED blood levels, vigilance states and others. In order to be able to compare different studies on seizure prediction, it is mandatory to define some standards on how to evaluate the performance of a seizure prediction algorithm (Mormann et al., 2007).

The performance of a detection or prediction algorithm is typically assessed in terms of the sensitivity and specificity of the warnings that are issued. The first thing to define is a prediction horizon, i.e., the time interval after a warning within which the seizure is expected to occur. The sensitivity of an algorithm can then be quantified as the percentage of seizures that occurred within the prediction horizon of a preceding warning (Fig. 3). Its specificity should be quantified as the percentage of time of the seizure-free interval during which no (false) warnings were active. The time basis used to quantify the specificity should include only time intervals during which a false warning can actually occur and should exclude preictal periods.

Once the performance of an algorithm has been assessed, one needs to determine whether this performance is indeed better than a chance prediction. For this purpose various statistical validation schemes have been proposed. These validation schemes are based either on quantifying the expected performance of a random predictor (Schelter et al., 2006; Snyder et al., 2008; Winterhalder et al., 2003; Wong et al., 2007) or on generating surrogate realizations of certain features of the algorithm's output via constrained randomization (Andrzejak et al., 2003, 2009; Kreuz et al., 2004), e.g. by randomly shuffling the output classifications of interictal and preictal time windows.

A common mistake in seizure prediction studies is the use of in-sample optimization and subsequent comparison of the optimized performance to a random predictor, such as testing only the performance of the best EEG channel. While it may be justified to train an algorithm for an individual patient, its performance should be tested only on data that was not previously used in the training process ('out-of sample testing').

For practical purposes, any algorithm can be reduced to a form in which a warning light is assumed to be either on or off. Any seizure occurring while the light is on is counted as correctly predicted. The overall percentage of time that the warning light was on can then be used to determine if the number of correctly predicted seizures exceeds the one expected by chance by calculating the probability that this outcome occurred by chance according to a simple binomial test (Mormann, 2008):

$$P(N, S, q) = \sum_{K \geq S} \binom{N}{K} q^K (1-q)^{N-K}$$

where q is the percentage of time the warning light is on, S is the number of seizures predicted, and N is the total number of seizures.

Despite retrospective evidence that a preictal state is present in many patients (Mormann et al., 2005), none of the studies on seizure prediction published to date have produced valid evidence that a warning algorithm can perform above chance level prospectively. Accordingly, participants in an ongoing seizure prediction competition (Schelter et al., 2010) so far have not been able to predict seizures in a quasi-prospective setting better than a random prediction scheme. The current literature is at best inconclusive as to whether or not seizures are predictable by prospective algorithms, although several commercial companies are currently developing proprietary algorithms. Statistical validation will be indispensible to answer this important question. A major step in this direction will be the use of datasets that are strictly split into training and testing sets, a necessary prerequisite to apply seizure prediction algorithms in a true prospective online fashion. Seizure databases such as this, combined with these statistical tests of performance, will allow rigorous testing of the seizure prediction algorithms currently under development using the technology and neurophysiological analyses described in the earlier sections.

Discussion

There is great interest in developing methods to detect seizures and predict them before they occur. Although the mechanisms of seizure generation are still unknown, there is evidence that measurable changes occur prior to seizures (Mormann et al., 2005), which lends hope that ongoing strategies will be successful. Stringent statistical studies have questioned the highly positive results of early seizure prediction studies that were based on the analyses of limited, if any, interictal periods. Nevertheless, several studies have demonstrated measurable changes in the preictal period. These methods may indicate brain states that have a higher probability of producing seizures, but in current form they are insufficient to meet the needs of patients, who desire much better specificity and sensitivity in a seizure prediction device (Schulze-Bonhage et al., 2010). Obviously, there is further need to improve seizure prediction algorithms and the methods of implementing them in a clinical device.

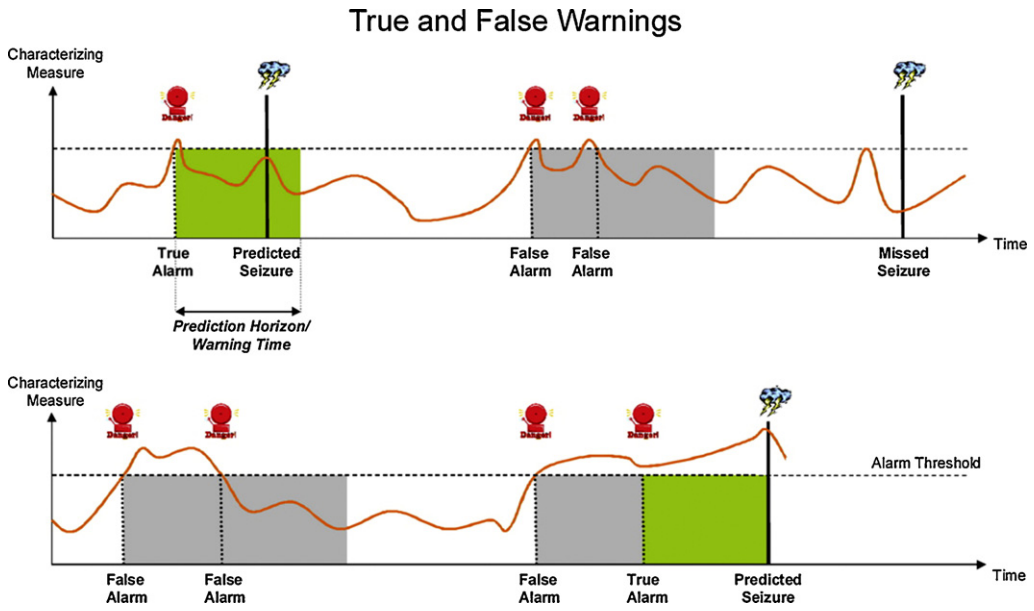

Figure 3 Whenever the time profile of some characterizing measure rises above a pre-defined threshold, the prediction algorithm issues an alarm which is classified as true or false, depending on whether or not it is followed by a seizure within a specified warning time, termed prediction horizon. The area shaded in gray represents the time during which the patient is under false warning, i.e. awaiting a non-occurring seizure. The area shaded in green represents the time under correct warning. In principle, alarms are issued continuously for as long as the measure profile remains above the threshold. For better legibility not all of these continuous alarms are shown. For the last seizure, alarms begin too early with respect to the prediction horizon so they are classified as false warnings until the seizure falls within the prediction horizon. The time period shown on the *x*-axis could typically represent 1 day (Mormann, 2008). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

Improvements in electrode design will have a major impact on spatial sampling fidelity, as clinical systems utilize smaller electrodes capable of reaching the level of individual cortical columns or even individual neurons. Furthermore, amplifiers with wide recording bandwidth and progress in digital signal analysis allow detailed analysis from very low frequencies to several thousand Hz. Thus, DC changes in early phases of seizures, and the topographies and temporal expression of high frequency oscillations and even unit potentials can be evaluated. The impact on seizure prediction is only now emerging — such as the presence of ''microseizures'' that appear to coalesce into clinically manifest seizures, or studies exploring the relationship between high frequency oscillations and epileptic tissue. Technology thus unveils new pathophysiological hypotheses that may lead to novel clinical applications.

Even with these optimistic developments in mind, a realistic assessment of the performance of seizure prediction methods is necessary to avoid a misjudgment on the present state of the art. Seizure prediction is very difficult, especially in light of the many confounding variables such as medications, fluctuating patient state, seizure heterogeneity, and the inherently stochastic nature of these events. When analyzed in a rigorous fashion with long datasets, no algorithm has yet been able to predict seizures better than chance or to detect periods of an increased probability for seizure occurrence. Is this because we have not yet discovered how to measure the physiological processes that lead to the ictal state? Does success require higher sampling resolution? Is prediction even possible? Researchers in this field are encouraged by objective evidence of preictal changes (Mormann et al., 2005) as well as abundant clinical experiences of patients who are able to predict their own seizures. One clear step forward has been to define a method to validate predictive performance statistically. Technological, clinical, and neurophysiological advances are now in place to develop and test new methods within this framework, using collaborative efforts such as seizure databases and the regular meetings of the International Seizure Prediction Workshop. Current work relating HFOs to seizures is encouraging and needs to be incorporated with the other techniques discussed herein for seizure prediction. HFOs are a promising candidate presently, and in the future hopefully the technologies and techniques discussed herein will help uncover additional neurophysiological phenomena to help us understand seizure generation. Success will depend upon continued collaboration among multiple clinical and basic science disciplines, as we attempt to use technology to help the millions of patients worldwide with intractable epilepsy.

References

Abend, N.S., Gutierrez-Colina, A., Zhao, H., Guo, R., Marsh, E., Clancy, R.R., Dlugos, D.J., 2011. Interobserver reproducibility of electroencephalogram interpretation in critically ill children. J. Clin. Neurophysiol. 28, 15—19.

Alarcon, G., Binnie, C.D., Elwes, R.D., Polkey, C.E., 1995. Power spectrum and intracranial EEG patterns at seizure onset in partial epilepsy. Electroencephalogr. Clin. Neurophysiol. 94, 326—337.

Allen, P.J., Fish, D.R., Smith, S.J., 1992. Very high-frequency rhythmic activity during SEEG suppression in frontal lobe epilepsy. Electroencephalogr. Clin. Neurophysiol. 82, 155—159.

Andrzejak, R.G., Mormann, F., Kreuz, T., Rieke, C., Kraskov, A., Elger, C.E., Lehnertz, K., 2003. Testing the null hypothesis of the nonexistence of a preseizure state. Phys. Rev. E: Stat. Nonlinear Soft Matter Phys. 67, 010901.

Andrzejak, R.G., Chicharro, D., Elger, C.E., Mormann, F., 2009. Seizure prediction: any better than chance? Clin. Neurophysiol. 120, 1465—1478.

Bagshaw, A.P., Jacobs, J., LeVan, P., Dubeau, F., Gotman, J., 2009. Effect of sleep stage on interictal high-frequency oscillations recorded from depth macroelectrodes in patients with focal epilepsy. Epilepsia 50, 617—628.

Benbadis, S.R., LaFrance Jr., W.C., Papandonatos, G.D., Korabathina, K., Lin, K., Kraemer, H.C., 2009. Interrater reliability of EEG-video monitoring. Neurology 73, 843—846.

Blanco, J.A., Stead, M., Krieger, A., Viventi, J., Marsh, W.R., Lee, K.H., Worrell, G.A., Litt, B., 2010. Unsupervised classification of high-frequency oscillations in human neocortical epilepsy and control patients. J. Neurophysiol. 104, 2900—2912.

Bragin, A., Mody, I., Wilson, C.L., Engel Jr., J., 2002. Local generation of fast ripples in epileptic brain. J. Neurosci. 22, 2012—2021.

Bragin, A., Wilson, C.L., Almajano, J., Mody, I., Engel Jr., J., 2004. High-frequency oscillations after status epilepticus: epileptogenesis and seizure genesis. Epilepsia 45, 1017—1023.

Crepon, B., Navarro, V., Hasboun, D., Clemenceau, S., Martinerie, J., Baulac, M., Adam, C., Le Van Quyen, M., 2010. Mapping interictal oscillations greater than 200 Hz recorded with intracranial macroelectrodes in human epilepsy. Brain 133, 33—45.

Della Marca, G., Vollono, C., Barba, C., Filomena Fuggetta, M., Restuccia, D., Colicchio, G., 2007. High-frequency ECoG oscillations in the site of onset of epileptic seizures during sleep. Sleep Med. 8, 96—97.

Diekelmann, S., Born, J., 2010. The memory function of sleep. Nat. Rev. Neurosci. 11, 114—126.

Dümpelmann, M., Kerber, K., Jacobs, J., Schulze-Bonhage, A.,2010. Automatic detection of intracranially recorded high-frequency oscillations using a radial basis function neural network gives reliable information about the distribution of HFOs over anatomical regions. In: Abstract, 64th Annual Meeting of the American Epilepsy Society. American Epilepsy Society, San Antonio, TX.

Engel Jr., J., Bragin, A., Staba, R., Mody, I., 2009. High-frequency oscillations: what is normal and what is not? Epilepsia 50, 598—604.

Fisher, R.S., Webber, W.R., Lesser, R.P., Arroyo, S., Uematsu, S., 1992. High-frequency EEG activity at the start of seizures. J. Clin. Neurophysiol. 9, 441—448.

Gardner, A.B., Worrell, G.A., Marsh, E., Dlugos, D., Litt, B., 2007. Human and automated detection of high-frequency oscillations in clinical intracranial EEG recordings. Clin. Neurophysiol. 118, 1134—1143.

Ihle, M., Feldwisch-Drentrup, H., Teixeira, C.A., Witon, A., Schelter, B., Timmer, J., Schulze-Bonhage, A., 2010. EPILEPSIAE — a European epilepsy database. Comput. Methods Programs Biomed..

Jacobs, J., Zelmann, R., Jirsch, J., Chander, R., Dubeau, C.E., Gotman, J., 2009. High frequency oscillations (80—500 Hz) in the preictal period in patients with focal seizures. Epilepsia.

Jirsch, J.D., Urrestarazu, E., LeVan, P., Olivier, A., Dubeau, F., Gotman, J., 2006. High-frequency oscillations during human focal seizures. Brain 129, 1593—1608.

Jiruska, P., Csicsvari, J., Powell, A.D., Fox, J.E., Chang, W.C., Vreugdenhil, M., Li, X., Palus, M., Bujan, A.F., Dearden, R.W., Jefferys, J.G., 2010. High-frequency network activity, global increase in neuronal activity, and synchrony expansion precede epileptic seizures in vitro. J. Neurosci. 30, 5690—5701.

Kelly, R.C., Smith, M.A., Samonds, J.M., Kohn, A., Bonds, A.B., Movshon, J.A., Lee, T.S., 2007. Comparison of recordings from microelectrode arrays and single electrodes in the visual cortex. J. Neurosci. 27, 261—264.

Kim, D.H., Viventi, J., Amsden, J.J., Xiao, J., Vigeland, L., Kim, Y.S., Blanco, J.A., Panilaitis, B., Frechette, E.S., Contreras, D., Kaplan, D.L., Omenetto, F.G., Huang, Y., Hwang, K.C., Zakin, M.R., Litt, B., Rogers, J.A., 2010. Dissolvable films of silk fibroin for ultrathin conformal bio-integrated electronics. Nat. Mater. 9, 511—517.

Kreuz, T., Andrzejak, R.G., Mormann, F., Kraskov, A., Stogbauer, H., Elger, C.E., Lehnertz, K., Grassberger, P., 2004. Measure profile surrogates: a method to validate the performance of epileptic seizure prediction algorithms. Phys. Rev. E: Stat. Nonlinear Soft Matter Phys. 69, 061915.

Le Van Quyen, M., Bragin, A., 2007. Analysis of dynamic brain oscillations: methodological advances. Trends Neurosci. 30, 365—373.

Le Van Quyen, M., Khalilov, I., Ben-Ari, Y., 2006. The dark side of high-frequency oscillations in the developing brain. Trends Neurosci. 29, 419—427.

Le Van Quyen, M., Staba, R., Bragin, A., Dickson, C., Valderrama, M., Fried, I., Engel, J., 2010. Large-scale microelectrode recordings of high-frequency gamma oscillations in human cortex during sleep. J. Neurosci. 30, 7770—7782.

Lehnertz, K., Litt, B., 2005. The First International Collaborative Workshop on Seizure Prediction: summary and data description. Clin. Neurophysiol. 116, 493—505.

Maiwald, T., Winterhalder, M., Aschenbrenner-Scheibe, R., Voss, H.U., Schulze-Bonhage, A., Timmer, J., 2004. Comparison of three non-linear seiuzre prediction algorithms by means of the seizure prediction characteristic. Physica D 194, 357—368.

Mormann, F., 2008. Seizure Prediction. www.scholarpedia.org/article/seizure_prediction.

Mormann, F., Kreuz, T., Rieke, C., Andrzejak, R.G., Kraskov, A., David, P., Elger, C.E., Lehnertz, K., 2005. On the predictability of epileptic seizures. Clin. Neurophysiol. 116, 569—587.

Mormann, F., Andrzejak, R.G., Elger, C.E., Lehnertz, K., 2007. Seizure prediction: the long and winding road. Brain 130, 314—333.

Quiroga, R.Q., Reddy, L., Kreiman, G., Koch, C., Fried, I., 2005. Invariant visual representation by single neurons in the human brain. Nature 435, 1102—1107.

Quiroga, R.Q., Mukamel, R., Isham, E.A., Malach, R., Fried, I., 2008. Human single-neuron responses at the threshold of conscious recognition. Proc. Natl. Acad. Sci. U. S. A. 105, 3599—3604.

Ritaccio, A., Brunner, P., Cervenka, M.C., Crone, N., Guger, C., Leuthardt, E., Oostenveld, R., Stacey, W., Schalk, G., 2010. Proceedings of the first international workshop on advances in electrocorticography. Epilepsy Behav. 19, 204—215.

Schelter, B., Winterhalder, M., Maiwald, T., Brandt, A., Schad, A., Schulze-Bonhage, A., Timmer, J., 2006. Testing statistical significance of multivariate time series analysis techniques for epileptic seizure prediction. Chaos 16, 013108.

Schelter, B., Feldwisch-Drentrup, H., Timmer, J., Gotman, J., Schulze-Bonhage, A., 2010. A common strategy and database to compare the performance of seizure prediction algorithms. Epilepsy Behav. 17, 154—156.

Schevon, C.A., Thompson, T., Hirsch, L.J., Emerson, R.G., 2004. Inadequacy of standard screen resolution for localization of seizures recorded from intracranial electrodes. Epilepsia 45, 1453—1458.

Schevon, C.A., Ng, S.K., Cappell, J., Goodman, R.R., McKhann Jr., G., Waziri, A., Branner, A., Sosunov, A., Schroeder, C.E., Emerson, R.G., 2008. Microphysiology of epileptiform activity in human neocortex. J. Clin. Neurophysiol. 25, 321—330.

Schevon, C.A., Trevelyan, A.J., Schroeder, C.E., Goodman, R.R., McKhann Jr., G., Emerson, R.G., 2009. Spatial characterization

of interictal high frequency oscillations in epileptic neocortex. Brain 132, 3047—3059.

Schevon, C.A., Goodman, R.R., McKhann Jr., G., Emerson, R.G., 2010. Propagation of epileptiform activity on a submillimeter scale. J. Clin. Neurophysiol. 27, 406—411.

Schulze-Bonhage, A., Sales, F., Wagner, K., Teotonio, R., Carius, A., Schelle, A., Ihle, M., 2010. Views of patients with epilepsy on seizure prediction devices. Epilepsy Behav. 18, 388—396.

Sejnowski, T.J., Destexhe, A., 2000. Why do we sleep? Brain Res. 886, 208—223.

Snyder, D.E., Echauz, J., Grimes, D.B., Litt, B., 2008. The statistics of a practical seizure warning system. J. Neural. Eng. 5, 392—401.

Stacey, W.C., Litt, B., 2008. Technology insight: neuroengineering and epilepsy-designing devices for seizure control. Nat. Clin. Practice 4, 190—201.

Stacey, W.C., Lazarewicz, M.T., Litt, B., 2009. Synaptic noise and physiological coupling generate high frequency oscillations in a hippocampal computational model. J. Neurophysiol. 102, 2342—2357.

Stacey, W.C., Krieger, A., Litt, B., 2011. Network recruitment to coherent oscillations in a hippocampal computer model. J. Neurophysiol. 105, 1464—1481.

Stead, M., Bower, M., Brinkmann, B.H., Lee, K., Marsh, W.R., Meyer, F.B., Litt, B., Van Gompel, J., Worrell, G.A., 2010. Microseizures and the spatiotemporal scales of human partial epilepsy. Brain.

Steriade, M., Contreras, D., Amzica, F., Timofeev, I., 1996. Synchronization of fast (30—40 Hz) spontaneous oscillations in intrathalamic and thalamocortical networks. J. Neurosci. 16, 2788—2808.

Traub, R.D., Whittington, M.A., Buhl, E.H., LeBeau, F.E., Bibbig, A., Boyd, S., Cross, H., Baldeweg, T., 2001. A possible role for gap junctions in generation of very fast EEG oscillations preceding the onset of, and perhaps initiating, seizures. Epilepsia 42, 153—170.

Truccolo, W., Donoghue, J.A., Hochberg, L.R., Eskandar, E.N., Madsen, J.R., Anderson, W.S., Brown, E.N., Halgren, E., Cash, S.S., 2011. Single-neuron dynamics in human focal epilepsy. Nat. Neurosci. 14, 635—641.

Vargas-Irwin, C.E., Shakhnarovich, G., Yadollahpour, P., Mislow, J.M., Black, M.J., Donoghue, J.P., 2010. Decoding complete reach and grasp actions from local primary motor cortex populations. J. Neurosci. 30, 9659—9669.

Viventi, J., Kim, D.H., Moss, J.D., Kim, Y.S., Blanco, J.A., Annetta, N., Hicks, A., Xiao, J., Huang, Y., Callans, D.J., Rogers, J.A., Litt, B., 2010. A conformal, bio-interfaced class of silicon electronics for mapping cardiac electrophysiology. Sci. Transl. Med. 2, 24ra22.

Winterhalder, M., Maiwald, T., Voss, H.U., Aschenbrenner-Scheibe, R., Timmer, J., Schulze-Bonhage, A., 2003. The seizure prediction characteristic: a general framework to assess and compare seizure prediction methods. Epilepsy Behav. 4, 318—325.

Wong, S., Gardner, A.B., Krieger, A.M., Litt, B., 2007. A stochastic framework for evaluating seizure prediction algorithms using hidden Markov models. J. Neurophysiol. 97, 2525—2532.

Worrell, G.A., Parish, L., Cranstoun, S.D., Jonas, R., Baltuch, G., Litt, B., 2004. High-frequency oscillations and seizure generation in neocortical epilepsy. Brain 127, 1496—1506.

Worrell, G.A., Gardner, A.B., Stead, S.M., Hu, S., Goerss, S., Cascino, G.J., Meyer, F.B., Marsh, R., Litt, B., 2008. High-frequency oscillations in human temporal lobe: simultaneous microwire and clinical macroelectrode recordings. Brain 131, 928—937.