Journal of Neuroscience Methods 260 (2016) 270–282

Contents lists available at ScienceDirect

Journal of Neuroscience Methods

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

Invited review

Seizure prediction for therapeutic devices: A review

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ARTICLE INFO

Article history:
Accepted 11 June 2015
Available online 19 June 2015

Keywords:
Seizure prediction
Focal epilepsy
Therapeutic devices
Statistical validation
Algorithms
Intracerebral EEG

ABSTRACT

Research in seizure prediction has come a long way since its debut almost 4 decades ago. Early studies suffered methodological caveats leading to overoptimistic results and lack of statistical significance. The publication of guidelines addressing mainly the question of performance evaluation and statistical validation in seizure prediction helped revising the status of the field. While many studies failed to prove that above chance prediction is possible by applying these guidelines, other studies were successful. Methods based on EEG analysis using linear and nonlinear measures were reportedly successful in detecting preictal changes and using them to predict seizures above chance. In this review, we present a selection of studies in seizure prediction published in the last decade. The studies were selected based on the validity of the methods and the statistical significance of performance results. These results varied between studies and many showed acceptable levels of sensitivity and specificity that could be appealing for therapeutic devices. The relatively large prediction horizon and early preictal changes reported in most studies suggest that seizure prediction may work better in closed loop seizure control devices rather than as seizure advisory devices. The emergence of a large database of annotated long-term EEG recordings should help prospective assessment of prediction methods. Some questions remain to be addressed before large clinical trials involving seizure prediction can be carried out.

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http://dx.doi.org/10.1016/j.jneumeth.2015.06.010
0165-0270/

1. Introduction

For decades, treatment options for epilepsy remained mainly pharmacological and to lesser extent surgical. Antiepileptic drugs have limitations (Deckers et al., 2003) and fail to control seizures in roughly 20–30% of patients. Advances in neuroimaging, electrode technologies and computerized surgical planning helped in better management of intractable seizures by reducing their severity and frequency, and in some cases by attaining seizure freedom. Patients who do not respond to medication and who are not candidates for surgery are in need of new treatment options. Recently, new lines of therapeutic treatment have emerged. Devices based on electrical stimulation (or neuromodulation) (Fisher, 2012), drug-delivery (Bennewitz and Saltzman, 2009; Fisher and Ho, 2002; Stein et al., 2000) and focal-cooling (Fujii et al., 2010; Rothman, 2009) have proven levels of efficacy in controlling seizures. Stimulation devices in particular have been thoroughly investigated. While their mechanisms of therapeutic action remain generally unexplained, evidence of their antiepileptic effects is supported by series of large controlled clinical trials (DeGiorgio et al., 2013; Fisher et al., 2010; Fregni et al., 2006; Heck et al., 2014; Morrell, 2011; Rong et al., 2014). Most of these devices administer continuous stimulation. The responsive neurostimulator system (RNS®) by NeuroPace, Inc. (Mountain View, CA, USA) delivers stimulation only when a seizure activity is detected from chronic EEG recordings. This type of intervention, known as closed-loop stimulation, has arguably an advantage over the continuous stimulation, mainly because less stimulation is used, which improves the power efficiency of the device and reduces side effects of long term stimulation (Springer et al., 2006).

Stimulation is thought to be more effective in abating seizures when it is administered earlier than later, before the onset of a seizure (Motamedi et al., 2002; Murro et al., 2003), but an optimum time at which stimulation is most effective has yet to be identified. This is true for most of the therapeutic modalities and it is mostly due to the lack of a full understanding of ictogenesis mechanisms. Electrical stimulation based on early seizure detection techniques has shown promising results in stopping seizures a few seconds after the electrographic onset (Fountas et al., 2005; Kossoff et al., 2004; Osorio et al., 2005). Closed-loop interventions from seconds to hours before the electrographic or clinical seizure onset are investigational. Such a therapeutic approach relies in principle on a sensitive and specific prediction of seizure occurrences to achieve seizure control and to minimize side effects from unnecessary interventions. The possibility of seizure prediction was explored for over 25 years, typically from EEG analysis. In most of the early studies, the main question was whether changes in the EEG preceding seizure onset could be identified. Measures derived from linear and non-linear analysis were reportedly successful in detecting changes minutes to hours before seizure onset (Lehnertz, 2001). The optimistic results of these studies were regarded as a proof-of-concept of the existence of a preictal state. The question of seizure predictability remained open though as the specificity of the preictal changes was not assessed. The first studies to evaluate specificity on controlled data were retrospective. Many showed methodological flaws largely related to optimization problems (in-sample data used in optimization and testing) and lack of statistical validation (superiority to random prediction) rendering the prediction power of many measures questionable.

The requirements for an acceptable range of sensitivity and specificity are not standard and depend on the clinical application. Nearly all published methods of seizure prediction are not tailored towards specific interventional devices. Their performance could not be assessed independently from a clinical context. In an attempt to define a maximum rate for false predictions, the patient's seizure frequency under epilepsy monitoring settings was used as a reference (Aschenbrenner-Scheibe et al., 2003; Winterhalder et al., 2003). Since an average of 3.6 seizures per day (equivalently 0.15 seizures per hour) are recorded during epilepsy monitoring (Haut et al., 2002), false prediction rates above 0.15/h are deemed questionable, at least outside of closed-loop intervention systems.

To assure methodological quality and practical assessment of seizure prediction methods, guidelines and statistical frameworks have been proposed (Andrzejak et al., 2003, 2009; Kreuz et al., 2004; Mormann et al., 2005, 2007; Snyder et al., 2008; Winterhalder et al., 2003; Wong et al., 2007). A number of studies proposing new seizure prediction methods have been carried out on the basis of these recommendations aiming for reliable prediction and clinically useful performance. In this review we present studies on seizure prediction published in the last decade (between January 1st 2004 and December 31st 2014) in peer-reviewed journals and listed in PubMed (Only PubMed search engine was used for retrieval of clinically relevant studies. Key term "seizure prediction" was used in the search). We further restricted the review to studies based on intracranial EEG recordings that attempted to demonstrate statistical significance of the reported performance results using recommended statistical validation procedures. Studies that were previously reviewed in Mormann et al. (2007) are not discussed. Levels of sensitivity and specificity varied between studies. Their usefulness depends on the clinical application. Studies based on scalp EEG analysis are arguably less applicable to chronic interventional devices and are not presented in this review.

2. Requirements of a practical seizure prediction method

The guidelines proposed by Mormann et al. (2007) tackled two major methodological issues in seizure prediction: whether the claimed prediction power of a seizure prediction method could

be demonstrated prospectively and if it is superior to chance. Ruling out random prediction is crucial because a random predictor often demonstrates above zero levels of sensitivity and specificity. This baseline performance is the minimum performance that a seizure prediction algorithm needs to beat in order to claim a significant prediction power. Statistical validation methods based on naïve prediction schemes (e.g. random predictors) (Mormann et al., 2006b; Schelter et al., 2006) or on Monte Carlo simulations (e.g. surrogate measures) (Andrzejak et al., 2003) could be used to test the superiority to chance, although the latter need to be used with caution as they can erroneously lead to invalid specificity results if an inappropriate null hypothesis is used for testing (Feldwisch-Drentrup et al., 2011).

Ideally, the prediction power of an algorithm should be demonstrated through prospective randomized controlled tests (class I evidence), generally conducted in clinical trials. To justify such trials, robust performance should first be demonstrated in a quasi-prospective setting using long-lasting, continuous and unseen EEG recordings. It is important that the recordings cover all possible physiological (e.g. state of vigilance, circadian variations) and pathological (level of medication) states of a patient in order to prove that seizure prediction works round the clock (Lehnertz et al., 2007). Test data should be independent from any training data that is used to train and optimize the algorithm.

The performance of an algorithm should be reported in terms of sensitivity and specificity on the test data. While the sensitivity is unequivocally defined as the proportion of true predictions, the specificity could be reported with different measures. The most common are the false prediction rate and the proportion of time under false warning. Snyder et al. (2008) proposed the proportion of time spent in warning and the warning rate as specificity-related metrics. As there is no consensus on which specificity measure is to be used, direct comparison between algorithms may not be straightforward.

Sensitivity and specificity are to be reported for the period of time during which a seizure is to be expected, known as the *seizure prediction horizon* (SPH) or the *seizure occurrence period* (SOP). Alarms followed by a seizure occurrence within the seizure prediction horizon count for true predictions whereas those that are not followed by a seizure occurrence count for false predictions. During the prediction horizon, data processing is normally halted and resumes at the end of the prediction horizon duration. In another scheme proposed by Snyder et al. (2008), the data is continuously processed during the prediction horizon. If a new alarm condition is detected within the prediction horizon, the prediction horizon duration is restarted. The proportion of time under warning can be illustrated by a warning light that is on whenever an alarm is active. If the light is on, say, 70% of the time, then this also the sensitivity expected by chance. Whether an observed sensitivity significantly exceeds this chance level, can be assessed using a simple binomial test (cf. Mormann, 2008).

For seizure prediction dedicated to interventional devices, the minimum *intervention time* (IT) has been defined as the minimum interval between an alarm and the beginning of the prediction horizon (Winterhalder et al., 2003). This interval of low likelihood of seizure occurrence guarantees a minimum time window for the therapeutic intervention and it is used as an additional constraint when evaluating the prediction algorithm performance.

3. Recently published seizure prediction studies

Seizure prediction methods can vary widely given the abundance of signal processing, mathematical and statistical tools that could be applied to the problem of tracking preictal changes from EEG time series. It is perhaps the type of EEG features and the way they are tracked that characterizes most a prediction algorithm. Features could be linear, non-linear, univariate (single channel) or multivariate (multiple channels) and can be tracked for preictal changes through profile thresholding or using machine learning tools (classifiers). Here, the studies are grouped in 4 categories based on the type and domain of analysis. Features used in each study, characteristics of the prediction method and its validation and EEG data used are summarized in Table 1. Since most of these studies used data from the Freiburg Seizure Prediction EEG database (FSPEEG, Winterhalder et al., 2003), we briefly outline the content of this database.

3.1. The Freiburg seizure prediction EEG database

The FSPEEG was proposed in the early 2000s as an EEG database available for download to researchers working primarily on seizure prediction. The database contains intracerebral (grid, strips and depth electrodes) EEG recordings from 21 patients with medically intractable focal epilepsy. The recordings were acquired with a 128 channel EEG system at 256 Hz sampling rate. At least 24 h continuous (in 13 patients) and discontinuous (in 8 patients) interictal recordings and 50 min preictal recordings are available from three focal and three extra-focal electrode contacts. Each patient had 2 to 5 preictal recordings (mean 4.2). Altogether, the database contained 582 h of EEG data, including preictal recordings of 88 seizures. Since 2012, the FSPEEG has been discontinued to be complemented and replaced by the larger EPILEPSIAE database (Ihle et al., 2012; Klatt et al., 2012) which contains datasets of annotated long-term scalp and intracranial EEG recordings from 275 patients.

3.2. Studies based on time-domain and pattern-based features

Time domain features measure entities of the EEG signal that depend only on time. Classical and advanced signal analysis techniques were used to derive a wide range of time domain features capable of characterizing linear and non-linear behaviors in the EEG and proving useful to seizure prediction. In a broad sense, time domain features describe three aspects of the signal: 1-amplitude, 2-variability and regularity and 3-synchronicity. Combination of features representing one or more of these aspects in univariate or multivariate measurements has led to many algorithms.

3.2.1. Ngram-derived pattern recognition for the detection and prediction of epileptic seizures (Eftekhar et al., 2014)

Based on pattern recognition, a novel method for detecting and predicting seizures was presented and tested using the Freiburg database. The method uses a symbolic data analysis of the EEG based on N-gram modeling—a probabilistic pattern recognition technique which identifies and predicts the occurrence of symbolic data sequences within data (Banerjee and Pedersen, 2003; Bengio et al., 2003). The data was first preprocessed using a 50 Hz notch filter and a smoothing filter to remove artifacts, then re-quantized from 16 to 8 bits to be adapted to the N-gram algorithm. Using a 1-min sliding window, the N-gram algorithm looks for repeating patterns by iteratively assessing the similarity between patterns of different sizes using an inverse Hamming distance. The sequence of the repeating patterns counts were then tracked for a fixed-(based on standard deviation of the background) and a dynamic-(based on the moving average of the pattern count) threshold crossing to generate warnings. Threshold values, the number of repeating patterns and the pattern length were optimized during training using 1 seizure and 1 h of interictal data from each patient. Three intervention time values (10, 20 and 30 min) and 2 seizure prediction horizon values (10 and 20 min) were analyzed. Of the 6 available channels, only the 3 seizure onset channels were analyzed. The authors performed what appears to be a cross-validation on the dataset and reported the average performance across iterations

Table 1
Seizure prediction studies with statistically validated results, published between 2004 and 2014.

Year	Authors	Features	Preictal change tracking method	Database	Patients	Seizures	EEG (h)	Statistical validation method
2014	Bandarabadi et al.	Bivariate spectral power	Classification (support vector machine algorithm)	EPILEPSIAE	24*	183	3565	Comparison with analytical random predictor
2014	Moghim et al.	34 (reduced to 14) univariate features	Classification (support vector machine algorithm)	FSPEEG	21	See database description		Comparison with baseline and random predictors
2014	Eftekhar et al.	Repeating EEG patterns	Threshold crossing	FSPEEG	21	87	623	Comparison with a random predictor
2014	Aarabi et al.	Univariate computational model parameters	Rule based decision	FSPEEG	21	87	596	Comparison with random and periodical predictors
2014	Zheng et al.	Bivariate mean phase coherence	Threshold crossing	FSPEEG	10	50	221.1**	Comparison with random predictor
2013	Li et al.	Spike rate	Threshold crossing	FSPEEG	21	See database description		Comparison with random predictor
2013	Gadhoumi et al.	Wavelet energy and entropy	Linear discriminant analysis	Montreal Neurological Institute	17	175	1565	Comparison with random predictor
2013	Cook et al.	Average Energy, Teager–Kaiser energy, line-length	Classification (decision tree and k-nearest neighbors algorithm)	Melbourne	11	***	****	Comparison with random predictor
2012	Williamson et al.	Time delayed univariate and multivariate correlations	Classification (support vector machine algorithm)	FSPEEG	19	83	448.3**	Comparison with chance level using area under ROC
2012	Aarabi et al.	6 non-linear features (5 univariate and 1 bivariate)	Threshold crossing and rule-based decision	FSPEEG	11	49	267**	Comparison with random and periodical predictors
2012	Park et al.	Univariate spectral power	Classification (support vector machine algorithm)	FSPEEG	18	80	433.2**	Comparison with random predictor
2011	Kuhlmann et al.	Bivariate mean phase coherence	Fixed and dynamic threshold crossing	Freiburg/Melbourne	6	73	597.6	Poisson process predictor and alarm time surrogates
2009	Mirowski et al.	6 linear and non-linear bivariate features	Classification using logistic regression, convolution networks and SVM	FSPEEG	21	See database description		Seizure time surrogates
2006	Sackellares et al.	Short-term maximum Lyapunov exponent	Dynamic threshold crossing	Gainesville	10	130	2100	Comparison with random and periodical predictor

* 8 of 24 had intracranial EEG recordings. Intracranial EEG recording time: 1401.6 h. Number of intracranially recorded seizures: 79.
** Interictal data.
*** Number of clinical seizures in training: 302, and in testing: 597.
**** Recordings during 90.7 to 467.9 days in the training phase, and during 4 months in the testing phase.

and channels. The method achieved a sensitivity of 67% for temporal lobe cases and a false prediction rate of 0.04/h for a seizure prediction horizon of 20 min and combined intervention time values. Frontal lobe cases showed lower specificity performance with 72% sensitivity and a false prediction rate of 0.61/h. By increasing the number of seizures in training, the method achieved significantly higher performance than with default setting, with up to 100% sensitivity and a false prediction rate of 0.06/h for the temporal cases. All results were significantly higher than chance level by comparison with a random predictor. Prediction time was not reported.

3.2.2. Epileptic seizure prediction using phase synchronization based on bivariate empirical mode decomposition (Zheng et al., 2014)

The authors proposed a method based on the mean phase coherence (MPC). MPC was originally proposed by Mormann et al. (2000) as a measure of phase synchronization and was found to decrease before seizure onset (Mormann et al., 2003b). The authors reported however that the predictive power of MPC did not exceed random levels and postulated that this may be due to the admixture of relevant and artifactual components in the EEG. To improve the performance of MPC, a bivariate empirical mode decomposition of EEG channels (Huang et al., 1998) was used. Pairs of EEG channels were simultaneously decomposed into oscillatory components called intrinsic mode functions. MPC was then calculated for each channel pair using a Hilbert transform as in Mormann et al. (2003b) in a moving window with 20 s width and 20% overlap (75 pairs of MPC measures for each window). Time profiles of MPC were analyzed for preictal changes. The method was optimized and tested using data from 10 patients in the Freiburg database. A leave one out five-fold cross validation was performed and the best three features (channel-pairs) exhibiting sensitive and specific preictal changes through threshold crossing of MPC profiles were selected. Using a cross-validation on the entire dataset, the authors assessed the performance of the method by using the seizure prediction characteristic for a range of maximum false prediction rates, seizure prediction horizon values, and minimum intervention time values. Preictal changes were detected 30 min before seizure onset. The levels of performance achieved were on average higher than those of a random predictor and the ones achieved by the method proposed by Mormann et al. (2003b). For a maximum false prediction rate of 0.15/h, the average sensitivity ranged between 25 and 70% when the seizure prediction horizon varied between 2 and 40 min, respectively, and the intervention time was fixed at 10 min. It is unfortunate that the authors did not report the performance results on an independent test data, hence deviating from the recommended guidelines of Section 2. The question whether an above-chance performance could indeed be achieved with this method must thus be regarded as still open.

3.2.3. Seizure prediction using spike rate (Li et al., 2013)

Motivated by the work of Lange et al. (1983) demonstrating preictal changes in the occurrence rate of epileptic spikes, and the work of Truccolo et al. (2011) demonstrating changes in neuronal spiking before seizure onset in focal epilepsy, the authors investigated the rate of epileptic spikes in intracranial EEG as a measure for seizure prediction. Using the Freiburg database, they divided the data into training and testing subsets. Spikes were detected using morphological filter after removal of high frequency artifacts (using a 0.5–30 Hz band-pass filter). The spike rate was found to be significantly different for the interictal, preictal, ictal and postictal segments when calculated on randomly selected 5 s epochs in each segment. It was then used as feature for prediction. For each channel, it was calculated in a 5 s sliding window and smoothed using a 30 s moving average filter. Alarms were generated when the smoothed spike rate of any channel crossed a patient-specific threshold optimized during training. Tested using an intervention time of 10 s, the algorithm achieved 56% sensitivity and a false prediction rate of 0.15/h for a seizure prediction horizon of 30 min and 72.7% sensitivity and a false prediction rate of 0.11/h for a seizure prediction horizon of 50 min. All these results were demonstrated to be above chance level. The authors compared the performance of their algorithm with methods based on dynamical similarity index, correlation dimension and accumulated energy presented in Maiwald et al. (2004), and with phase synchronization (Winterhalder et al., 2006a) and convolutional networks combined with wavelet coherence (Mirowski et al., 2009). The proposed algorithm outperformed these methods in terms of sensitivity and/or specificity when tested on the same database. The authors reported an average sensitivity of 75.8% and a false prediction rate of 0.09/h across 21 patients but they did not provide the seizure prediction horizon and intervention time values used to get these results. The mean prediction time was 49.7 min.

3.2.4. Seizure prediction using EEG spatiotemporal correlation structure (Williamson et al., 2012)

A method combining patient-specific machine learning and multivariate features was presented. The features were based on the eigenspectra of space—delay correlation and covariance matrices computed at multiple time delays. Data from 19 patients of the Freiburg database were selected to evaluate the method. First, the data was normalized (zero mean and unit variance) to control for different power levels between channels, then filtered using a 0.5–120 Hz band-pass and a 50 Hz notch filter. A total of 488 features were extracted in 15 s epochs from the EEG channels. They were normalized (zero mean and unit variance) to allow for relative comparison with the baseline then reduced into decorrelated feature set using principal component analysis (PCA) where the 20 top components were computed from the training set and used later in testing. A support vector machine (SVM) based classifier was trained using cross-validation. The output of the classifier was temporally averaged over a 15 min window to reduce the prediction noise and used as a prediction score. The authors assessed the sensitivity and specificity based on threshold crossing of the prediction score and a seizure prediction window equivalent to the seizure prediction horizon. They used alarm retriggering within the seizure prediction window following Snyder et al. (2008) and reported the specificity in terms of warning rate and proportion of time spent in warning. When default parameters were used (seizure prediction window = 30 min), the algorithm achieved remarkably high performance values. For 3 prediction threshold values, the average sensitivity varied between 86% and 95%, the proportion of time spent in warning between 9% and 3%, and the warning rate between 0.07/h and 0.03/h. Using a receiver operating characteristic (ROC) sensitivity analysis, the algorithm performance was found higher than the chance performance. The area under the ROC curve (AUC) was 0.973 for the default parameters compared to 0.5 for chance performance. The authors explored the impact of varying different parameters (epoch duration, number of delay scales, number of principal components and covariance feature variations) on the algorithm performance as measured by the AUC and found that default parameters produced the best results. It was unclear if this investigation was carried out on the training or on the testing dataset. Preictal changes were detected 25 to 30 min prior to each seizure in one patient.

3.2.5. A rule-based patient-specific seizure prediction method for focal neocortical epilepsy (Aarabi and He, 2012)

The authors presented an extension of their previously published study (Aarabi and He, 2011) to a larger group of patients. The patient-specific algorithm was developed based on a

combination of non-linear univariate and bivariate features that have been investigated in previous studies and shown to carry predictive power. The authors used intracranial EEG datasets from 11 patients with neocortical epilepsy selected from the Freiburg database, thus selecting "a more challenging seizure prediction problem" to solve and a "more common type of focal epilepsy" (Aarabi and He, 2012). Data was split into an optimization subset containing a 50-min preictal segment and a 4 h interictal segment per patient, and a testing subset containing the rest of EEG segments available. To reduce data variability, the authors performed a cross-validation analysis on the optimization and testing interictal data and reported the average performance over trials in each patient. The algorithm had 3 stages: preprocessing, feature extraction and rule-based decision-making. First EEG segments were filtered using a 0.5–100 Hz band-pass and 50 Hz notch filtering. Five univariate measures, namely correlation dimension, correlation entropy, noise level, Lempel–Ziv complexity, and largest Lyapunov exponent and one bivariate measure, nonlinear interdependence, were extracted from each channel separately in non-overlapping 10 s epochs. The measures were normalized and smoothed via a 5 min averaging window. Channels in which training preictal data exhibited values one standard deviation above or below the interictal baseline were selected for testing. Spatiotemporal information from all features was then extracted from the test segments and compared with the training preictal segment in order to detect seizure precursors using 4 threshold values and a set of combination and integration rules. An alarm was raised only if 4 consecutive windows were flagged as seizure precursors. Thresholds were optimized through a ROC analysis of the training data. Finally, the sensitivity was compared with that obtained using random and periodical predictors in order to statistically validate the method. Using an intervention time of 10 s and two seizure prediction horizon values, 30 and 50 min, an average sensitivity of 79.9% and 90.2%, an average false prediction rate of 0.17 and 0.11/h, and an average specificity of 97% (defined as the proportion of correctly classified interictal segments of the length of a seizure occurrence period) were, respectively achieved. The portion of time under false predictions was close to 4% and the mean minimum prediction time was close to 13 and 24 min, respectively. The authors reported the performance of each feature used individually and concluded that the combination of univariate and bivariate measures contributed to performance improvement by minimizing false predictions caused by isolated single-channel seizure precursors. Preictal changes were found in channels of the epileptogenic and remote areas.

3.2.6. *Patient-specific bivariate-synchrony-based seizure prediction for short prediction horizons (Kuhlmann et al., 2010)*

The authors investigated a measure previously proposed by Schelter et al. (2006), the bivariate synchrony. Compared to analysing a subset of channels as in the original study, they analyzed all available channels from long-term intracranial recordings (grids, subdural strips and depth electrodes) from 6 patients with intractable focal epilepsy. Two statistical validation methods were investigated to assess the superiority to chance: analytical Poisson predictor (Schad et al., 2008; Schelter et al., 2006) and alarm time surrogates (Andrzejak et al., 2009). The mean phase coherence proposed by Mormann et al. (2000) was calculated from pairs of EEG channels as a measure of bivariate synchrony. Different window lengths were investigated and data smoothing with a median filter was explored. Increases and decreases of the MPC time sequence were investigated for predictability power in each pair of channels using a set of seizure prediction horizon values (0.67, 2 and 5 min) and relatively short periods of intervention time (1, 3, 5, 10 and 15 min). Four thresholding techniques using fixed and dynamic threshold values were then applied to generate alarms. For each MPC analysis window and thresholding technique, the prediction performance was evaluated for channel pairs using a single parameter, defined as the area above the ROC curve and below the unit sensitivity line. Comparing the performance of the top 5% channel pairs in the proposed method and in a Poisson based random predictor, the method failed to prove superiority to chance. However, there was always a subset of parameters for which the performance of the best channel pair was better than the Poisson based predictor. The authors argued that using the analytical Poisson process to assess the statistical validation of the results has caveats, mainly due to wrong assumption that channel pairs provide statistically independent prediction times. They proposed the use of bootstrapping methods instead. Alarm time surrogates were then used to assess statistical significance of a 4-fold out-of-sample cross-validation analysis applied to the best channel-pairs. Here, the authors used channel pairs selected within-sample on the same data they use to assess performance, which warns against overestimated results and makes it impossible to judge whether their algorithm would still have performed above chance level during out-of-sample testing. Instead, the best channels could have been re-selected in the training part of each iteration of the analysis to avoid any possible in-sample optimization. The authors reported that the cross-validation performance results for most patients were reasonable. The best sensitivity for each patient ranged from 50 to 88% and the corresponding false prediction rates ranged from 0.64 to 4.69 1/h. Such relatively high false prediction rates are beyond the proposed maximum rate of 0.15/h and may hinder the usefulness of the proposed method in clinical applications.

3.2.7. *Predictability analysis for an automated seizure prediction algorithm (Sackellares et al., 2006)*

This study evaluated a seizure prediction method that was previously presented in a series of publications (Chaovalitwongse et al., 2005; Iasemidis et al., 2003a, 2003b, 2005; Pardalos et al., 2004). The authors used a database of intracerebral continuous EEG with 130 seizures from 10 patients with intractable mesial temporal lobe epilepsy. EEG was sampled at 256 Hz and filtered between 0.5 and 70 Hz. Convergence in short-term maximum Lyapunov exponent (STLmax) – a measure of the local chaoticity in a dynamical system – was used for tracking preictal changes in critical electrode sites. The epileptic brain was hypothesized to "progress into and out of order–disorder states according to the theory of phase transitions of nonlinear dynamical systems" (Iasemidis and Sackellares, 1996). STLmax was calculated from the available 60 channels every 10.24 s. The first seizure and its 10 peri-ictal minutes were used for training the algorithm and selecting the best groups of channel pairs based on a similarity index of postictal and preictal profiles of STLmax. Three groups (of 3 channels each) with the highest difference between postictal and preictal T-index profiles calculated over 10 min period were selected and continuously monitored for critical threshold crossings, dynamically adapted to detect a preictal state—referred to as *entrainment* state. An alarm was then triggered for the duration of a seizure prediction horizon. The authors evaluated the performance of the method as a function of the seizure prediction horizon (referred to as *seizure warning horizon* by the authors), between 30 min and 3 h. For seizure prediction horizon values above 30 min, the method outperformed random predictors, when the performance was measured by the area above the ROC curve of the sensitivity analysis. For a seizure prediction horizon of 30 min, the across-patients average sensitivity reached 80% and the false prediction rate was 0.56/h. The mean seizure warning time was 13.3 min. The false prediction rate dropped to 0.12/h when the seizure prediction horizon was set to 150 min. The fraction of time under false warning ranged from 28.3% (seizure prediction horizon = 30 min) to 32.1% (seizure prediction horizon = 150 min). Prediction time depended on the

seizure prediction horizon value and ranged between 13.3 and 90.2 min on average (respectively, for seizure prediction horizon values between 30 and 180 min). Note that the same algorithm had previously been published on the same data set, but without a proper statistical validation (Chaovalitwongse et al., 2005; Mormann et al., 2006a; Winterhalder et al., 2006b). In the current study, the method was compared with two naïve prediction schemes (random and periodic prediction) for statistical validation and was reported to beat chance in both cases. However, this assessment of performance was carried out including the training data so the true out-of-sample performance remains elusive. In addition, false prediction rates were underestimated since the authors did not take into account that false predictions by definition cannot occur during the seizure prediction horizon. Finally, no statistical hypothesis testing was carried out. Instead the biased in-sample performance of the algorithm was shown to merely beat the chance predictors on average. Given these methodological shortcomings, it remains unclear whether the reported algorithm indeed performs above chance level. The authors discussed the potential use of this method in epilepsy monitoring units or in closed-loop seizure control devices while acknowledging that prospective testing was needed to confirm its clinical utility.

3.3. Studies based on frequency domain and time-frequency analysis based features

Frequency domain features are derived from the spectral content of the EEG obtained by transformation of the time-domain signal. The main spectral feature is the spectral power, often defined as the statistical estimate of the signal power in each frequency component and referred to as the spectral power density. The PSD has been extensively used in EEG analysis to identify and classify activities and states. Time-frequency analyses such as wavelet analysis allow to resolve the spectral content with some temporal resolution. Features extracted in the time-frequency domain provide information about the spectral and temporal content simultaneously and have been widely used in the tracking of spectral changes in EEG time series for a variety of applications.

3.3.1. Epileptic seizure prediction using relative spectral power features (Bandarabadi et al., 2015)

This study presents an algorithm based on spectral power ratios. The authors trained and tested the algorithm on long-term continuous datasets from 24 patients of the EPILEPSIAE database (183 ictal events in 3565 h). Of the 24 patients, 8 had intracranial EEG sampled at 400 Hz or 1024 Hz. Channels from 3 electrodes in the seizure onset area and 3 in remote areas were analyzed. The recordings were notch-filtered at 50 Hz. Normalized spectral power of the EEG standard spectral bands (Delta, Theta, Alpha, Beta, and Gamma), were calculated for each channel in a 5 s moving window. The authors introduced the ratio between normalized spectral powers to track preictal changes. It quantifies the cross spectral power between two spectral bands of two channels. The ratio was calculated for all combinations of channels and EEG spectral bands. Four hundred and thirty five ratios were then computed and smoothed in 1-min averaging window to reduce the effect of artifacts. A feature selection procedure based on the maximum difference in amplitude distribution histograms (MDADH) of preictal and non-preictal samples (Teixeira et al., 2011) reduced the number of ratios to use for testing. An SVM classifier was trained using a subset of data after balancing the number of interictal and preictal samples for unbiased classification. The authors dedicated the first 3 seizures for training and the remaining seizures for testing. Contrasting with many seizure prediction studies, the authors optimized the value of the seizure prediction horizon in training. Four seizure prediction horizon values (10, 20, 30 and 40 min) were analyzed for best performance. The seizure prediction horizon value and the SVM model corresponding to a maximum sensitivity and minimum false positive rates were selected for classification of test data. The classifier's output was regularized using a firing power measure (Teixeira et al., 2011) then normalized and monitored for threshold crossing to generate alarms. The algorithm performance proved superior to chance by comparison with an analytical random predictor. Performance results were reported separately for patients with scalp and intracranial EEG. On average across the 8 patients with intracranial EEG, the algorithm achieved 78.36% sensitivity and 0.15/h false prediction rate for an average seizure prediction horizon of 33.7 min. These results were comparable to those obtained with scalp data. The average number of features selected was 9.9. It was smaller for intracranial than for scalp data. The authors commented that intracranial EEG carries clearer and more localized epileptogenic information than scalp EEG, therefore less discriminant features may be needed for the optimum results. The time of the first preictal change leading to a seizure (*prediction time*) was not reported.

3.3.2. Seizure prediction based on measures of state similarity (Gadhoumi et al., 2013)

This study presented an algorithm based on measures of similarity between preictal and interictal states derived from wavelet entropy and energy. The ability of these measures to discriminate preictal and interictal periods was demonstrated in an earlier publication (Gadhoumi et al., 2012). Wavelet energy and entropy were calculated from continuous wavelet transform of EEG segments selected in the preictal (~20 min), immediate preictal (90 s) and interictal periods in 4 frequency bands (between 50 and 450 Hz, 100 Hz bandwidth). Three *state similarity* measures – the *inclusion*, the *persistence* and the *distance* – quantifying the similarity of EEG epochs with the immediate preictal epoch were introduced based on the wavelet energy and entropy. A discriminant analysis combined with a cross-validation procedure was performed on a channel-by-channel basis in the training phase to select the frequency band and channels that yielded the best classification results using state similarity measures calculated over EEG epochs. The algorithm was tested on a database of continuous long-term intracerebral EEG (1565 h, 175 seizures) from 17 patients with mesial temporal lobe epilepsy consecutively selected at the Montreal Neurological Hospital. Unlike the Freiburg database, these recordings were acquired continuously over days. The statistical framework proposed by Snyder et al. (2008) was applied to evaluate the performance of the algorithm as a function of the *persistence*–τ parameter, which is equivalent to the sum of seizure prediction horizon and intervention time. The algorithm predicted seizures above chance in 7 of 17 patients, for persistence–τ values above 30 min. The mean sensitivity was higher than 85%, the mean proportion of time under warning was less than 30%, and the mean warning rate was less than 0.35/h. The average false prediction rate was below 0.1/h and the median prediction time was around 36 min. The authors found that patients with a history of status epilepticus showed better results than those with no history of status epilepticus. They pointed, however, to the relatively small cohort analyzed and the need for further validation of such a new finding.

3.3.3. Prediction of seizure likelihood with a long-term, implanted seizure advisory system in patients with drug-resistant epilepsy: A first-in-man study (Cook et al., 2013)

The study presented the assessment results of safety and efficacy of a seizure advisory system implanted in 15 adult patients with drug-resistant focal epilepsy, having between 2 and 12 seizures per month. After surgical implantation of the device, the patients entered a data collection phase in which a seizure prediction algorithm was established for each patient and individually trained

using the patient's collected data. Over one month of EEG recordings containing a minimum of 5 lead seizures (defined as clinical seizures preceded by a minimum of 8 h of interictal data) were used to develop a patient's algorithm. The algorithm identified periods of high, moderate, and low seizure likelihood. Upon completion of the data collection phase, only patients for whom the sensitivity of high-likelihood warnings was greater than 65% and the performance was better than chance prediction were selected for a next phase to receive advisory information about seizure likelihood through a portable device. Of the 15 implanted patients, 11 progressed to the advisory phase. Clinical effectiveness and performance of the seizure prediction algorithm were then tested prospectively for a period of 4 months.

The prediction algorithm was developed based on a purpose-built cluster-computing environment. Three layers were used: filtering, features extraction, and classification. Intracranial EEG signals from 16 channels were filtered using octave-wide digital filters between 8 and 128 Hz, wide-band filters and optional notch filters to eliminate AC main sources. Filtered signals were then analyzed over a 5 s analysis window to extract the average energy, the Teager–Kaiser energy, and the line-length, which were then normalized using previously derived parameters or by other signals. In total, 288 features (16 channels × 6 filter/normalization options × 3 features) were extracted. Using a backward feature elimination technique based on Hilbert–Schmidt Independence Criterion (BAHSIC), the feature set was reduced to 16 features which were subsequently used for the classification. The classifier involved multiple (10) layers inspired from a decision-tree and a k-nearest neighbor (kNN) classifier. The classifier output was a measure of a seizure risk. The output was filtered, thresholded, and then passed to a user interface state machine used to control the three seizure likelihood indicators (high, moderate, and low). The performance of the algorithm was assessed using a leave-one-out cross-validation in the data collection (training) phase. The sensitivity (for the high-likelihood advisory) and the percentage time under low and high advisories were used as performance metrics. The authors argued that percentage time under low and high advisories are better measures of specificity than the conventional specificity which would "subjectively be based on an arbitrarily chosen prediction horizon". The significance of the advisory performance was assessed by comparing the sensitivity with that of a time-matched chance indicator (Snyder et al., 2008).

The authors reported the prospective performance at 4 months of the advisory (testing) phase using the same metrics they used in training. They also reported the likelihood ratios to compare seizure rates between high and low-likelihood advisories. Only clinical seizure events or events with similar electrographic patterns to clinical seizure events were considered in the assessment. The statistical performance of 10 out of the 11 patients advancing to the 4-month advisory phase could be assessed, and 9 of them showed a prospective performance significantly above chance level. A sensitivity of 100% was achieved in 2 patients. The mean warning time of the high seizure likelihood advisory was 114 min.

This study was the first and only to date to demonstrate truly prospective seizure prediction and using ambulatory intracranial EEG data. The authors reported that the algorithm performance was maintained through the training phase and the 4 months long advisory phase. Periodic retraining was found necessary, however, to maintain or improve the performance. The authors highlighted the inconclusiveness of the clinical usefulness of seizure prediction and indicated that the high variability of seizure warning times prevented a uniform response among patients. Patients with the lowest proportions of time in the high-likelihood advisory were reportedly satisfied with the device and able to benefit from it.

Interestingly, the authors reported strong drifts of their feature vectors during the days after implantation of the device. This means that the performance of seizure prediction algorithms tested on data recorded in epilepsy monitoring units in a hospital setting might be systematically underestimated, since all publicly available data sets, including the Freiburg and the EPILEPSIAE databases, were acquired in such an environment. It would thus be desirable that this unique data set, recorded over months in an ambulatory setting, be made available to the seizure prediction research community at some point.

Another remarkable finding of this study was that seizure events reported by the patients and seizures actually captured on EEG were hardly correlated, raising doubts about the suitability of patient seizure diaries as a gold standard for assessing the success of any therapeutic procedure in epilepsy (Elger and Mormann, 2013).

3.3.4. *Seizure prediction with spectral power of EEG using cost-sensitive support vector machines (Park et al., 2011)*

The authors proposed a patient-specific method based on spectral features of intracranial EEG and machine learning which they trained and tested using data from 18 patients of the Freiburg database. The data was first preprocessed to remove power line noise around 50 Hz and 100 Hz using band-pass filters. Spectral power of 8 spectral bands (4 standard EEG bands and 4 wide gamma frequency bands, between 30 Hz and 128 Hz) and their total was calculated in a 20 s half overlapped moving window and normalized by the total power. To minimize the dominance of low frequency band power, a time-differential montage which normalizes the power across the spectrum was used. Time differentiation was applied to referential and bipolar recordings and spectral features were calculated for 4 montages (referential, referential/time differential, bipolar and bipolar/time-differential). A kernel Fisher discriminant analysis was used to determine the best feature set for testing. A cost-sensitive SVM classifier was then used to classify preictal and interictal test data based on selected features. The authors argued that a cost-sensitive SVM classifier has the advantage of handling the unbalanced number of preictal and interictal samples. To overcome over-fitting, they performed a double cross-validation on the entire dataset. For each patient, they divided the data into training and testing subsets and performed a cross-validation using the training subset to train the SVM classifier. The performance of the classifier was tested using the test subset. The entire dataset was then split again into randomly selected training and testing subsets and the process was repeated 5 times to perform a 5 fold cross-validation analysis in order to ultimately evaluate the performance of the classifier. The output of the classifier was smoothed using a Kalman filter to remove isolated false positives. An alarm was then raised for a seizure prediction horizon of 30 min (equal to the assumed preictal period) when the classifier output positive-crosses the zero baseline. Using the referential montage, the method achieved an average sensitivity of 98.3% and an average false prediction rate of 0.29/h across 18 patients. A slightly better performance was achieved using the bipolar montage. The false prediction rate decreased using time-differential montages while the sensitivity remained almost the same as with referential and bipolar montages. Overall the false prediction rate was higher than the proposed maximum rate value of 0.15/h. The authors estimated the one-sided p-value (Snyder et al., 2008) to assess the method's superiority to chance and demonstrated that above chance prediction could be achieved in 18 patients. The use of bipolar and time-differential preprocessing improved significantly the overall performance. Spectral power in gamma bands were found to be the most discriminating features in eight patients. The authors highlighted the low computational cost of the linear features employed in the method as an advantage for implantable devices. The

prediction time was not specified. The significance of this study is that to the best of our knowledge it was the first to convincingly demonstrate above-chance performance of a prediction algorithm in an out-of-sample setting with a fixed set of pre-optimized parameters.

3.4. Studies based on mixed time-domain and frequency-domain features

Studies based on both time-domain and frequency or time-frequency domain features often use a sizeable amount of features that capture different temporal and spectral aspects of the EEG and which do not provide satisfactory prediction results if used individually. In most cases, only a subset of features demonstrating a discrimination power between preictal and interictal states during the learning phase of the algorithm are individually selected by means of a feature selection procedure.

3.4.1. Predicting epileptic seizures in advance (Moghim and Corne, 2014)

An algorithm based on univariate features and machine learning, named Advanced Seizure Prediction via Pre-Ictal Relabeling (ASPPR), was trained and tested using the Freiburg database. The authors used 34 features (Costa et al., 2008) based on energy and on non-linear dynamics (the maximum Lyapunov exponents and correlation dimension). Fourteen of these features were used to compare the algorithm with algorithms that previously used these features. The remaining 20 features were based on EEG statistical descriptors, spectral band power calculated over standard EEG bands and spectral edge frequency. The features were extracted in 5 s non-overlapping windows in each of the 6 channels selected for each patient, then reduced to 14 features per channel using a feature selection procedure. The authors introduced a "*time-in-advance predictive model*" characterized by a "*time-in-advance*" parameter t. Such a model is learned during training and used to predict the occurrence of seizure onset between t and $t+5$ min. The parameter t was varied between 0 and 20 to make 21 prediction models to optimize. The terminology used by the authors is comparable to that used by the seizure prediction community: the time-in-advance parameter would translate to the minimum intervention time and the seizure prediction horizon would be fixed to 5 min. Also, varying the time-in-advance parameter would lead to establishing the *seizure prediction characteristic* as proposed by Winterhalder et al. (2003) and performing a sensitivity analysis. For each value of the intervention time equivalent parameter, a 10-fold cross validation technique (70% training and 30% testing) was performed. Learning the model parameters was based on multi-class SVM. Performance was evaluated on the testing data of each cross-validation trial and averaged across the trials. The authors reported the sensitivity, the specificity and the S1 score, defined as the geometric mean of sensitivity and specificity. Conventional specificity metrics (false prediction rate and the proportion of time under alarm/false alarm) were not reported. The algorithm outperformed unspecific predictors based on baseline and probabilistic schemes by demonstrating S1 scores, sensitivity and specificity levels significantly higher than achieved with the unspecific predictors. A relatively high specificity and accuracy (respectively, ~99% and ~97%) were achieved for all values of the intervention time equivalent parameter. The average sensitivity ranged between ~89% and 93.5%. Using the S1 score, the best prediction performance corresponded to $t=1$ (intervention time = 1 min). Of note, it would have been useful to report conventional specificity metrics. Prediction time was not reported, but it could be inferred from results that it is in the order of few minutes.

3.4.2. Classification of patterns of EEG synchronization for seizure prediction (Mirowski et al., 2009)

Machine learning-based classifiers using an aggregation of EEG bivariate measures were proposed for patient-specific seizure prediction. EEG data from the Freiburg database was divided into training and testing sets for each patient. The data was filtered between 0.5 and 120 Hz, and power line noise was removed. Then it was normalized either to have zero mean and unit variance or between −1 and 1 depending on the classification technique. Six bivariate measures proposed in previous studies were extracted for each pair of channels in a 5 s sliding window; cross correlation (Mormann et al., 2003a), nonlinear interdependence (Arnhold et al., 1999), dynamical entrainment (Iasemidis et al., 2005) and three features based on phase synchrony (Le Van Quyen et al., 2001, 2005). The measures were aggregated for the channel pairs and frequency bands to form 5-min long patterns of space, time and spectral profiles. Three machine-learning based classifiers, two based on neural network architecture (logistic regression and convolutional neural networks) and one based on support vector machines, were trained to distinguish between preictal and interictal segments in the training data subset. For each classifier, a feature selection was performed based on a sensitivity analysis. The authors first reported the test performance of each classifier and each feature separately in terms of sensitivity and false prediction rates. They found that for each patient, a 100% sensitivity and 0 false predictions could be obtained with at least one combination of classifier and feature. These results corresponded to a 2 h prediction horizon which was implicitly determined by the duration of the analyzed preictal period. Preictal changes were detected on average 60 min before the ictal onset. Across patients, the best results were obtained using convolutional networks based classifier combined with wavelet coherence with a 100% sensitivity and 0 false predictions for 15 of 21 patients. When using a subset of automatically selected features, it was found that 3 or 4 of 15 channel pairs were sufficient to reach optimal training results with non-frequency-based features (cross-correlation and nonlinear interdependence). Also, only a subset of frequency bands was discriminatory when using synchrony measures. All results were statistically validated by comparison to seizure time surrogates based random predictor. The authors reported that the method was not condition-specific as it did not work better for a particular patient's characteristic (surgery outcome, type of epilepsy, and location of epileptogenic zone) than another. A correction for multiple testing using all these different parameter combinations was not performed.

3.5. Studies based on computation models of neural activity

Neural computation models simulate the behavior of the neuronal activity by mathematical and computational processes in an attempt to describe the individual or collective neural mechanisms. Neural mass and neural field models have particularly helped elucidate the underlying general principles of EEG activity in a variety of physiological and pathological phenomena. Many neural mass models have been developed to simulate transitions to seizure (van Putten and Zandt, 2014 and references therein) and understand its dynamical processes. Application of such models to seizure prediction has been attempted in the early 2000s by (Schindler et al., 2002).

3.5.1. Seizure prediction in hippocampal and neocortical epilepsy using a model-based approach (Aarabi and He, 2014)

The study presents a seizure prediction algorithm based on a computational model where features are estimated from the model fit to EEG data. A neural mass model originally developed by (Lopes da Silva et al., 1974) to explain the origin of the alpha activity and later modified by Jansen and Rit (1995) was used. After

preprocessing the data through filtering operations, the model was fitted to the frequency spectrum of intracranial EEG segments using a Bayesian inference method (Moran et al., 2008). Twelve model parameters were estimated for each channel in a 10 s sliding window and used as predictive features. Their time profiles were smoothed using a 5-min moving-average window and normalized. Parameters and channels were labeled based on the results of the statistical comparison between a 50-min preictal and 4-h interictal segments in training. The spatiotemporal label profiles of the 12 parameters were then analyzed to establish patient-specific rules used to track recurrent patterns as they were observed in training. The method was evaluated using the Freiburg database with separation of testing set from the training set used for model fit and parameter adjustment. Statistical validation was carried out by comparing the method's sensitivity to that of a random and periodical predictors (Maiwald et al., 2004). Two seizure prediction horizon values were analyzed, 30 and 50 min. A minimum seizure prediction horizon (equivalent to IT) of 10 s was used. When tuned to maximize sensitivity, the system achieved an average sensitivity of 87.1% and 92.6% and an average false prediction rate of 0.2 and 0.15/h, for a seizure prediction horizon of 30 and 50 min, respectively. When tuned to maximize specificity, the sensitivity was 82.9% and 90% and the false prediction rate was 0.16 and 0.12/h for a seizure prediction horizon of 30 and 50 min, respectively. The average portion of time under false warning was remarkably low ($3.6 \pm 3.1\%$) but unclear if it was obtained with a seizure prediction horizon of 30 or 50 min. For both performance optimization strategies, the method is probably more clinically useful for a seizure prediction horizon of 50 than 30 min since the false prediction rate is below the maximum rate of 0.15/h considered clinically useful by some groups only for the former seizure prediction horizon. For both strategies, preictal changes were found on average 16 min before electrographic onset for a seizure prediction horizon of 30 min and 27 min for a seizure prediction horizon of50 min. These changes were independent of the location of electrodes.

4. Discussion

For many years research in seizure prediction lacked rules and guidelines that warrant a flawless methodology and prevent overoptimistic results. The recommendations made by Mormann et al. (2007) tackled the caveats observed in the design and evaluation of many seizure prediction methods. A consensus to consider these recommendations as guidelines for future seizure prediction studies was made by the research community following discussions and workshops. Many recent studies on seizure prediction correctly applied these guidelines. In this review, we summarized the methods and findings of these studies in an attempt to track the progress made in seizure prediction research in the last decade.

The advent of publically available databases of EEG recordings eased the direct comparison of performance results between studies. Since it was made available in 2004, the Freiburg database was extensively used in seizure prediction and detection based on invasive EEG analysis. Almost all studies presented in this review used this database. Despite being replaced by the larger and more comprehensive EPILEPSIAE database in 2012, the Freiburg database continues to be the material of many current publications (Aarabi and He, 2014; Eftekhar et al., 2014; Li et al., 2013; Moghim and Corne, 2014; Zheng et al., 2014). One limitation of the Freiburg database is the lack of information about the state of vigilance and level of medication in each patient. Given the well-established influence of such factors on the dynamics of the EEG (Kreuz et al., 2004; Lehnertz and Elger, 1997), such a limitation needs to be taken into account when assessing the prediction performance reported in the studies presented in this review. Changes in the state of vigilance, circadian fluctuations along with changes in medication levels during tapering should be considered when analyzing EEG data for seizure prediction. Schelter et al. (2011) reported that EEG measures may fluctuate with the vigilance state and lead to false alarms. Quantifying the influence of these changes on the performance of the algorithm could be challenging however (Mormann et al., 2005). In practice, evaluating a seizure prediction method on long term, continuous and uninterrupted EEG data covering all possible states and conditions of the patient should be sufficient to demonstrate its clinical usefulness (Lehnertz et al., 2007).

Another drawback of the Freiburg database is that interictal control data was typically recorded during the first 24 h of epilepsy monitoring, whereas seizures often occurred several days later and under different levels of medication. Thus a continuous algorithmic performance evaluation over several days is not possible. The recently completed EPILEPSIAE database (Ihle et al., 2012; Klatt et al., 2012) should help to overcome this limitation.

The guidelines proposed by Mormann et al. (2007) did not define what would be considered an acceptable performance in terms of sensitivity and specificity values. A minimum requirement was for a seizure prediction algorithm to prove superior to chance. Fulfilling this requirement may not justify prospective clinical trials on its own. A seizure prediction algorithm needs to demonstrate acceptable levels of sensitivity and specificity, which typically depend on the clinical application (Krieger and Litt, 2008). As performance requirements may vary between applications, it becomes difficult to define a gold standard for the required seizure prediction performance. Consequently, it is generally difficult to judge or compare the performance of currently published algorithms, assuming their design and statistical validity. Defining a limit for an acceptable false prediction rate based on the average seizure frequency in epilepsy monitoring setting was probably the only attempt to recommend explicit levels of specificity for seizure prediction algorithms. While in some studies the somewhat arbitrary value of 0.15/h, corresponding to a positive predictive value of 50% in a typical clinical setting, was considered as a benchmark in the evaluation of the performance, other studies did not question the relatively high false prediction rates they reported. In this context it is important to realize that the relative costs of a type I error ('false positive') and a type II error ('false negative' or 'miss') may vary considerably depending on the particular warning or intervention scenario. E.g. in a closed-loop intervention setting where electrical stimulation below the perceptual threshold succeeds in seizure prevention or abatement, higher false positive rates can be tolerated than in a case where the intervention is perceived as a negative side effect.

The conceptual issues of statistical validity and in-sample optimization have been addressed properly in many of the recent studies. The evaluation of the prediction performance however, was not standard and varied between studies. Some studies reported the specificity in terms of proportion of time under warning (or false warning), while others used the false prediction rate. The seizure prediction horizon and the minimum intervention time parameters have not been applied consistently in all studies. In fact, some studies considered only one parameter for the prediction horizon ignoring the minimum intervention time. Often, the performance was evaluated for one or two values of the seizure prediction horizon. Few studies applied the seizure prediction characteristic and evaluated their methods for different values of the seizure prediction horizon and/or minimum interventional time. On the other hand, trying out various values for the seizure prediction horizon corresponds to multiple testing, which needs to be accounted for by a correction for multiple comparisons in the statistical validation procedure. The freedom of using one's own performance metrics and parameters adds to the difficulty of unbiased comparison between methods. New guidelines for performance evaluation

in seizure prediction may be necessary and should alleviate such caveats.

Whether some approaches or measures are better than others in predicting seizures has long been debated. In a comparative study of 30 EEG measures, Mormann et al. (2005) suggested that the combination of univariate and bivariate EEG measures could be a promising approach for prospective seizure prediction. The study by Aarabi and He (2012) which combined non-linear univariate and bivariate features showed indeed relatively good prediction performance. Most of the studies in this review used only one feature variant however and many reported acceptable performance. Further investigation could be carried out in these studies to assess if their performance could be improved with combinations of univariate and bivariate features. The use of multivariate measures capturing the spatio-temporal dynamical changes was shown to be potentially promising for achieving high performance (Williamson et al., 2012).

The optimum results reported in (Mirowski et al., 2009) suggest that the combination of linear and nonlinear features derived from the temporal and spectral domain could lead to high prediction results, although for a relatively high prediction horizon (2 h). Given the lack of a demonstrated superiority for a particular type of feature (linear, nonlinear, temporal or spectral), the approach of combining all feature types may indeed lead to desirable results. Increasing the number of features did not appear to be particularly relevant though. Studies which used multiple features had comparable results with those which used few features, probably because features with no discriminant power are irrelevant and do not contribute to – or may reduce – the end performance. Likewise, the performance results reported in threshold-based and in machine learning-based studies were comparable. Many studies have particularly used SVM-based classifiers and reported relatively good performance results. While these classifiers are known for their robustness, the key to high prediction performance is primarily the choice of EEG features. Different seizure types are probably generated by different mechanisms which display various EEG manifestations of the interictal to preictal transition that may not all be detected and quantified with one single feature or feature type. Some features may work well for some patients and less so for others. This could partially explain why for example the mean phase coherence yielded encouraging results in (Mormann et al., 2003b) and an average performance in (Kuhlmann et al., 2010) due to high false prediction rates.

Physiologically motivated computational models of epilepsy open a new approach in seizure prediction. The study by Aarabi and He (2014) demonstrating acceptable results proved that model-based algorithms are worth investigating. The continuous refinement of computational neural models such as neural mass and neural field models should contribute to better characterization of the preictal dynamics and potentially lead to sophisticated model-based prediction algorithms and to a better understanding of the preictal state.

The significant progress made in seizure prediction in the last decade is yet to be corroborated by clinical trials. Prospective testing with long-term EEG recordings is a necessary but insufficient procedure to prove ultimate clinical utility. It could precede clinical trials to validate the performance of candidate algorithms. Large EEG datasets with comprehensive annotation as in the EPILEPSIAE database could be well suited for this step. Clinical experiments of seizure prediction begin to emerge. In a first-in-human study, Cook et al. (2013) demonstrated that seizures of patients with focal epilepsy could be anticipated by means of a chronically implanted device running a seizure prediction algorithm. Such results could open the door to larger studies involving seizure advisory devices where the goal is to warn the patients about upcoming ictal events just minutes before their occurrence. The relatively long prediction time reported in the reviewed studies may appeal better to closed-loop devices though. In fact, seven of the 12 studies which reported the prediction time found that preictal changes could be detected 13 min or more before onset. Depending on the seizure prediction horizon parameter, the prediction time may increase up to an hour. In a seizure control device, this would translate into a large intervention window which could potentially fit the requirements of a stimulation or a drug delivery procedure to alter the ictogenesis process and ultimately prevent a seizure from occurring (alternatively alleviating its manifestations). Long prediction horizons can also be useful in advisory systems tuned for high specificity where patients are provided with an assurance of seizure-free periods during the prediction horizon. Conversely, large prediction horizons are unpractical for warning patients who prefer to be advised only few minutes of an impending seizure (Schulze-Bonhage et al., 2010).

The efficacy of on-demand treatment devices to stop focal seizures rely on the spatial configuration of the sensing and treatment electrodes (Mormann et al., 2007). While target sites for effective stimulation in epilepsy are being identified (Fisher, 2012), areas of preictal changes are yet to be clearly determined. In partial epilepsy, such changes are probably local rather than widespread and the likelihood of detecting them may depend closely on the location and number of sensing channels. Contrasting findings about areas where preictal changes could be detected have been reported. The laterality of the preictal changes was reported in some of the reviewed studies: In general, electrodes implanted in the epileptogenic areas as well as in remote areas have equally been found to show preictal changes (Aarabi and He, 2011, 2014; Gadhoumi et al., 2013; Kuhlmann et al., 2010; Zheng et al., 2014). A better understanding of ictogenesis mechanisms could help identify areas of the brain where preictal changes are highly detectable, therefore guiding the placement of sensing electrodes in a seizure prediction based intervention device.

Among the reviewed studies, only few attempted to explain the possible neurophysiological mechanisms associated to the preictal changes in the EEG features. This is possibility due to the difficulty in the interpretation of some measures and/or to considering this interpretation unnecessary or irrelevant to a seizure prediction method. The interpretation of preictal changes is particularly challenging when multiple features are used. Preictal changes observed in the biophysical and physiological parameters of the neural model proposed by Aarabi and He (2014) provide in principle a possible explanation of the underlying neurophysiological changes they reflect. The study found however no consistent trend in the change of model parameters in many patients and did not discuss the neurophysiological meaning of these changes. Other studies interpreted the observed changes in the features as macroscopic changes in the synchrony of the brain state. Williamson et al. (2012) interpreted the increases and decreases in eigenvalue distributions of different energy modes prior to seizures as a reflection of greater or smaller synchrony preceding seizure onset. Other studies used the MPC as a direct measure of such synchrony (Kuhlmann et al., 2010; Zheng et al., 2014). Recent micro-electrode recordings of local field potentials and neuronal firing activity during seizure occurrence (Bower et al., 2012; Schevon et al., 2012; Truccolo et al., 2011) may also help improve our understanding of the neurophysiological mechanisms involved in seizure generation (Mormann and Jefferys, 2013).

5. Conclusion

Seizure prediction remains an active area of research with some questions yet to be answered before it flourishes as a breakthrough treatment in epilepsy. The tangible progress made in this field and the need of an alternative treatment to anti-epileptic drugs in

patients with intractable epilepsy should encourage the research community, the medical device and pharmaceutical industry and the funding bodies to join efforts and make a commercial seizure prediction device available to patients.

Acknowledgments

This work was supported by the Canadian Institutes of Health Research (CIHR) grants MOP-10189/102710, by the Royal Society of Canada and the Natural Sciences and Engineering Research Council of Canada (NSERC) grant CHRPJ 323490-06, and by the joint NSERC/CIHR grant CHRP-CPG-80098. Florian Mormann acknowledges support from the Lichtenberg Program of the Volkswagen Foundation and the German Research Council (SFB 1089).

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