Epilepsia, **(*):1–9, 2010
doi: 10.1111/j.1528-1167.2009.02497.x

FULL-LENGTH ORIGINAL RESEARCH

Joining the benefits: Combining epileptic seizure prediction methods

*†‡§Hinnerk Feldwisch-Drentrup, †¶Björn Schelter, *†‡Michael Jachan, †‡Jakob Nawrath, *†¶#Jens Timmer, and *‡Andreas Schulze-Bonhage

*Bernstein Center for Computational Neuroscience Freiburg, University of Freiburg, Freiburg, Germany; †Freiburg Center for Data Analysis and Modeling, University of Freiburg, Freiburg, Germany; ‡Epilepsy Center, University Hospital of Freiburg, Freiburg, Germany; §Department of Neurobiology and Biophysics, Faculty of Biology, University of Freiburg, Freiburg, Germany; ¶Department of Physics, University of Freiburg, Freiburg, Germany; and #Freiburg Institute for Advanced Studies, University of Freiburg, Freiburg, Germany

Summary

Purpose: In recent years, a variety of methods developed in the field of linear and nonlinear time series analysis have been used to obtain reliable predictions of epileptic seizures. Because individual methods for seizure prediction so far have shown statistical significance but insufficient performance for clinical applications, we investigated possible improvements by combining algorithms capturing different aspects of electroencephalogram (EEG) dynamics.

Methods: We applied the mean phase coherence and the dynamic similarity index to long-term continuous intracranial EEG data. The predictive performance of both methods was assessed and statistically evaluated separately, as well as by using logical "AND" and "OR" combinations.

Results: Used independently, either method resulted in a statistically significant prediction performance in only a few patients. Particularly the "AND" combination led to improved prediction performances, leading to an increase in sensitivity and/or specificity. For a maximum false prediction rate of 0.15/h, the mean sensitivity improved from about 25% for the individual methods to 43.2% for the "AND" and to 35.2% for the "OR" combination.

Discussion: This study shows that combinations of prediction methods are promising new approaches to enhance seizure prediction performance considerably. It allows merging the individual benefits of prediction methods in a complementary manner. Because either sensitivity or specificity of seizure prediction methods can be improved depending on the needs of the desired clinical application, the combination opens a new window for future use in a clinical setting.

KEY WORDS: Epilepsy, Seizure prediction, Prediction method combination.

Epilepsy, one of the most common chronic diseases of the central nervous system, affects 0.5–1% of the world's population (Hauser et al., 1996). Presently about one-third of all epilepsy patients cannot be treated adequately by continuous administration of antiepileptic drugs. Surgical resection of the epileptogenic nervous tissue is an option only for a subgroup of these patients. Hence, new means for the suppression of epileptic seizures are highly desired. A prediction of the time when epileptic seizures occur would not only allow warnings to the patients such that they could avoid potentially endangering situations, it would also open up new opportunities for closed-loop therapeutic strategies. Short-term intervention techniques could be used, including electroencephalogram (EEG)–controlled local application of anticonvulsant drugs (Stein et al., 2000), or closed-loop electrical brain stimulation (Li & Mogul, 2007).

During recent years, a number of prediction methods have been developed (Lehnertz & Elger, 1998; Martinerie et al., 1998; Le van Quyen et al., 1999; Mormann et al., 2000; Litt et al., 2001; Iasemidis et al., 2001; Schindler et al., 2002; Esteller et al., 2005; Iasemidis et al., 2005; Kalitzin et al., 2005; Le van Quyen et al., 2005; for recent reviews see Mormann et al., 2007; Sackellares, 2008). Based on linear and nonlinear time series analysis techniques, preseizure changes in the dynamics of intracranial and scalp EEG recordings have been examined and employed for seizure prediction. Evidence for the existence of a preseizure state has been given in several studies. Yet, retrospective studies that involved statistical validation and correction for

Accepted November 18, 2009; Early View publication Xxxx Xx, 200X.
Address correspondence to Hinnerk Feldwisch-Drentrup, FDM, Eckerstr. 1, 79104 Freiburg, Germany. E-mail: feldwisch@bccn.uni-freiburg.de; mail@hinnerkf.de

in-sample optimization reported significant seizure prediction performances only for a subset of all patients (Mormann et al., 2005; Schelter et al., 2006a). The observed interindividual variation in performance may be caused by diverse etiologies, exogenous triggers, and the inherent physiologic variability among patients.

Because several mechanisms may contribute to interictal–ictal transitions (Lopes da Silva et al., 2003a,b), it can be hypothesized that combinations of seizure prediction techniques may show performances that are superior to those of the individual methods. As suggested by Mormann et al. (2005), particularly the combination of univariate and bivariate methods could be an auspicious approach. These methods extract specific features, that is, time series containing data that are derived from one channel of the EEG, or from multiple channels, respectively. They may identify different aspects of the local and distributed brain dynamics contributing to a transition to ictal activity.

Using two prediction methods for which promising results were found in previous studies, herein we investigate different kinds of combinations. Two basic types of combinations were chosen following Boolean logic. For a logical ''AND'' combination, the individual methods have to trigger an alarm during a given time window to cause an alarm of the combined system. For a logical ''OR'' combination, each alarm of any of the individual methods is considered as an alarm of the combined system. Depending on the coincidence of alarms triggered by the individual methods, either of these combinations could provide particular advantages. Two methods with low specificity could be linked using the ''AND'' combination to select those predictions that are generated quasi-simultaneously by both methods. If correct predictions of both methods are strongly correlated, this is expected to reduce the number of false predictions considerably while preserving the sensitivity of the individual methods. The ''OR'' combination results in a unification of individual prediction methods, as all alarms of individual methods lead to alarms of the combined system. If, for example, each method is able to predict a specific seizure type with high sensitivity, a combination using a logical ''OR'' would match the correct predictions of both methods together. Because false alarms also add up, the ''OR'' combination would show its superiority if the increase in sensitivity outweighs a possible loss of specificity.

Herein we suggest an approach to optimize the combination of two seizure prediction techniques, resulting in one combined prediction system. Hereby, the combination can either be optimized for maximum sensitivity as pursued in this article, or also for maximum specificity, depending on the requirements of the desired intervention method. For statistical validation, the prediction performance is compared to a random predictor.

Materials and Methods

Applied individual prediction methods

In this study we investigated the seizure prediction performance of combinations of two previously introduced prediction methods, the mean phase coherence (MPC, Mormann et al., 2000) and the dynamic similarity index (SIM, Le van Quyen et al., 1999). The MPC is a measure of phase synchronization between pairs of electrode channels, for which preictal changes have been observed (Rosenblum et al., 1996; Mormann et al., 2000, 2003a,b, 2005; Le van Quyen et al., 2005; Winterhalder et al., 2006). The SIM is a univariate measure comparing ongoing EEG dynamic of one electrode channel to an interictal reference period thereof. Again, distinctive changes preceding epileptic seizures have been reported in several studies (Le van Quyen et al., 1999, 2000, 2001a,b; Navarro et al., 2002, 2005; Schelter et al., 2006b). Details about both methods are given in the Supporting Information.

The seizure prediction characteristic

To evaluate the performance of seizure prediction methods, the seizure prediction characteristic has been introduced (Winterhalder et al., 2003). It allows the assessment of the results of prediction methods depending on the prediction intervention time (IT), seizure occurrence period (SOP), and a maximum rate of false alarms (FPR_{max}). Alarms are issued when the feature time series falls below a threshold, which is optimized for the respective feature. The IT is defined as the minimum period of time between the alarm and the earliest possible occurrence of a subsequent seizure. In clinical applications, an intervention may be applied during this time window. Following the IT, an SOP is defined to limit the interval during which the seizure is expected to occur. The shorter the SOP, the more precise the prediction and the more limited is the time a patient is under alert for a predicted seizure.

In addition to the sensitivity—defined as the ratio of correctly predicted seizures to the number of seizures investigated—an assessment of the specificity of a certain prediction method by evaluating long-term interictal data is crucial (Winterhalder et al., 2003; Schelter et al., 2006a; Mormann et al., 2007). For this purpose, a maximum rate of tolerated false predictions FPR_{max} is predefined. In this study, we typically applied a maximum false prediction rate set to the average rate of clinical seizures, which is about 0.15 seizures per hour during presurgical monitoring (cf. Haut et al., 2002; Winterhalder et al., 2003). This ensures that on average no more false alarms are accepted than seizures occur.

In order to test whether an observed prediction performance is statistically significant, it has to be tested whether it is better than random. To this end, the seizure prediction characteristic was complemented by an analytical random predictor, which does not exploit any information contained

in the EEG data (Schelter et al., 2006a). The significance of prediction performances can then be assessed by comparing the observed sensitivity to the sensitivity of the random predictor, which is based on an identical FPR_{max} (cf. Supporting Information). If the observed sensitivity is indeed higher than the sensitivity of the random predictor, it is regarded as statistically significant.

To optimize prediction methods for individual patients, both the duration of the IT and the SOP can be varied. For the minimum duration of the preictal phase (IT), a wide range of values was reported in the literature (cf. Mormann et al., 2007). Therefore, an optimal IT was determined for each patient. The increased number of free optimization parameters was taken into account by the random predictor (for details see Supporting Information). After an alarm, no further alarms were considered within the ongoing IT and SOP.

Optimizing the combination of prediction methods

The thresholds for the features time series of each method were chosen such that the overall performance of the combination was optimal with regard to sensitivity while keeping to a predefined maximum false prediction rate FPR_{max}.

By the ''AND'' combination, an alarm is raised only if the features of both individual methods cross thresholds during a predefined time interval, the combination window (CW, cf. Fig. 1A). By the ''OR'' combination (Fig. 1B), each threshold crossing of each method triggers an alarm of the combination, again under the constraint that the temporal distance to the previous alarm must be larger than the duration of IT + SOP. Compared to a single prediction method, each additional method increases the number of free optimization parameters of the combination due to the additional thresholds, which can be chosen independently for each method. For the ''OR'' combination, the achieved sensitivity will be at least as good as the best of the individual methods, as thresholds of all other methods can be set to a value for which no alarms are raised. For the ''AND'' combination, this depends on the time course of the actual features.

In order to decrease combinatorial complexity, which is determined by the number of feature time series of the prediction methods that are combined, the first part of the data of each patient (including at least 36 h and at least three seizures) was used for a preselection. For both individual prediction methods, one optimal feature was determined, that is, the best channel combination for the MPC and the best channel for the SIM. This was performed by evaluating the sensitivity of all features, averaged over ITs and SOPs of 10, 20, …, 60 min each and based on a maximum false prediction rate of 0.15 false predictions per hour.

Both individual methods and their combinations were then evaluated on the remaining part of the data retrospectively. For fixed values of SOP and FPR_{max}, and for ITs of 10, 20, … 60 min, an optimal threshold was selected for the previously chosen features. This is a threshold value between zero and one, for which best sensitivity is observed, given a false prediction rate of less or equal to FPR_{max}. If for several thresholds the same optimal sensitivity was achieved, the threshold with the lowest observed false prediction rate was selected. For each type of combination, thresholds were optimized simultaneously for both features, and the ITs for which best sensitivities can be observed were determined. Finally, statistical significance was tested by comparison to the random predictor.

Patient characteristics and EEG database

Continuous intracranial long-term EEG recordings from eight patients with pharmacoresistant focal epilepsy were used in this study (Table 1). These were recorded during presurgical epilepsy monitoring at the Epilepsy Center of the University Hospital Freiburg, Germany. The retrospective evaluation of the data received prior approval from the ethics committee of the University of Freiburg Medical Faculty. Informed consent was obtained from each patient.

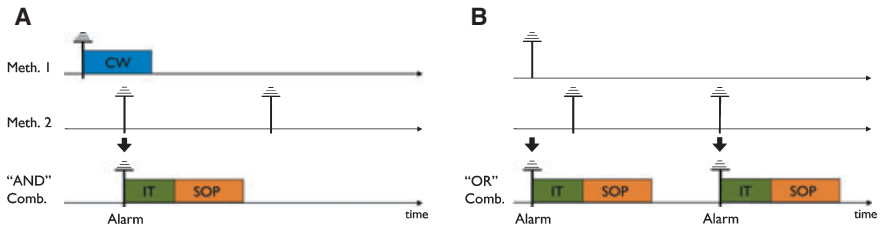

Figure 1.
Concept of the combination of prediction methods using a logical "AND" (**A**) and "OR" (**B**) for given alarms of two prediction methods (Meth. 1, 2). For the "AND" combination, an alarm of one of the methods is followed by a combination window (CW). Only if the other method triggers an alarm during this time interval, an alarm of the combination is raised. For the "OR" combination, each single alarm triggers an alarm of the combination. These alarms are followed by the intervention time (IT) and the seizure occurrence period (SOP). During the period of IT + SOP after an alarm, no further alarms are triggered.

Table 1. Patient and EEG data characteristics

Pat. no.	Age	Sex	Seizure type(s)	Seizure origin	Electrodes	Outcome	Recording length (h)	No of seizures	Feature selection	
									Length (h)	No. seizures
01	28	M	SP; CP	NC	g; s	Ib	204	25	36	5
02	50	M	SP; CP; GTC	H	g; s; d	Ib	241	14	36	3
03	31	F	SP; CP; GTC	NC	d; s	Ia	176	13	86	3
04	18	M	SP; CP; GTC	NC	g; s	Ia	148	19	36	10
05	11	M	SP; CP; GTC	H	d; s	Ia	187	26	91	3
06	42	F	SP	NC	g	Ic	159	17	36	5
07	35	M	SP; CP	NC + H	d; s	No surgery	179	17	70	3
08	21	M	SP; CP	NC + H	d; s	Ia	162	22	36	12
Ø							182.0	19.1	53.3	5.5

Seizure types: SP, simple partial; CP, complex partial; and GTC, generalized tonic–clonic. Seizure origin: NC, neocortical; and H, hippocampal. Intracranial electrodes: g, grid; s, strip; and d, depth. Outcome: according to a modified Engel classification (Engel & Rasmussen, 1993).

Table 2. Localization of electrode channels of the preselected features

Patient	1	2	3	4	5	6	7	8
MPC	f/e	e/e	f/e	f/e	f/f	e/e	f/f	f/e
SIM	e	e	e	f	e	e	f	e

For the bivariate mean phase coherence (MPC), these can either be focal/focal (f/f), focal/extrafocal (f/e) or extrafocal/extrafocal (e/e) channel combinations; for the univariate dynamic similarity index (SIM), either focal (f) or extrafocal (e) electrode channels exist.

EEG data were recorded using a Neurofile NT digital video EEG system (IT-Med, Usingen, Germany) with sampling rates of 256, 512, or 1024 Hz. Recordings were performed using subdural grid and strip electrodes with steel contacts of 2.3 mm diameter and/or depth electrodes with a contact diameter of 1 mm and a length of 5 mm (Ad-Tech®, Racine, WI, U.S.A.). The data were high-pass filtered at 0.5 Hz, low-pass filtered for anti-aliasing using a 97 Hz ± 15% (−3 dB) filter, and digitized with a 16 bit analog-to-digital converter. The EEG channels were referenced to the channel displaying lowest epileptic activity. A 50-Hz notch-filter was used to eliminate possible line noise. All features were calculated using sliding windows of fixed duration in time. Therefore, the number of data points varied between patients dependent on the sampling rates. For details, please refer to the Supporting Information.

For each patient, three electrode channels inside and three electrode channels outside the epileptic focal area were selected prior to any analysis by a certified epileptologist (ASB). Criteria for the selection were initial seizure activity for the focal channels, no or late involvement in ictal activity for the nonfocal channels, and good recording quality based on visual inspection and analysis performed during presurgical identification of the seizure onset zone. From these six channels, 15 bivariate features for the mean phase coherence and six univariate features for the SIM were calculated.

In total, 1,456 h of continuous recordings were analyzed in this study, varying between 148 and 241 h per patient. During these recordings, 153 seizures occurred, varying between 13 and 26 per patient. All seizures analyzed occurred spontaneously, but antiepileptic medication was reduced for the majority of patients during the recording period. The first part of the data of each patient was used for feature selection as described in the previous section. The optimization of the combinations based on the selected features was investigated afterwards on the remaining data, which on average for all patients included 13.6 seizures, ranging from 9–23, and a recording duration of 129 h, ranging from 91–205 h.

Results

Localization of preselected EEG channels

The localizations of the electrode channels of the preselected features are listed in Table 2. For the MPC, two focal–focal, two extrafocal–extrafocal, and four focal–extrafocal channel combinations showed best prediction performance. For the SIM, features derived from two focal and six extrafocal channels exhibited best predictive power. For two of the eight patients the electrode used for the SIM is used also for the MPC. With these preselected features, both individual methods and their combinations were analyzed based on the second part of the data.

Exemplary effects of combinations

Characteristic effects of combinations based on two features are shown in Fig. 2A,B for exemplary recording periods of patient 6. Optimal thresholds for the preselected features of the MPC and the SIM were determined such that

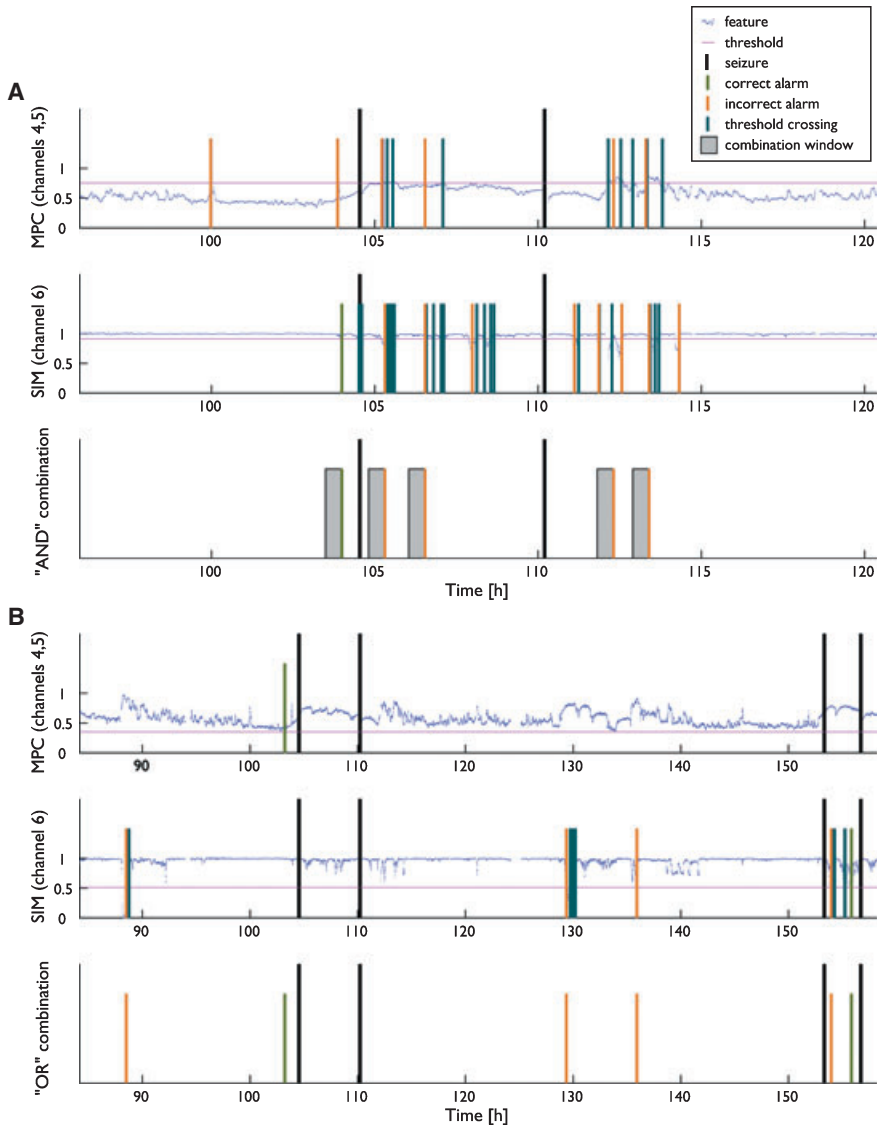

Figure 2.
Effects of the "AND" (**A**) and "OR" (**B**) combination on predictions (here: selected recording periods from patient 6). The time courses of the individual features are shown in blue for the mean phase coherence (MPC) in the top plot, and for the dynamic similarity index (SIM) in the middle plot. The thresholds (purple horizontal lines) for both methods were adapted such that the combinations (bottom rows) achieve optimal results. Black lines indicate seizures. Alarms were triggered if the features fall below the thresholds: green lines mark correct predictions, orange lines false ones, and blue-green vertical lines threshold crossings within IT + SOP following another alarm, which are not considered in the analysis. The combination windows of the "AND" combination are indicated in gray. The length of the combination window and the duration of the SOP was set to 30 min; FPR_{max} to 0.15 false predictions per hour. IT was 10 min for the "AND" combination; 50 min for the "OR" combination. Note that for the "AND" combination, an alarm is triggered only if an alarm of one method is followed by an alarm of the other within the combination window. For the "OR" combination, each threshold crossing of either method results in an alarm. IT, intervention time; SOP, seizure occurrence period.

the combinations achieve their best sensitivity given the predefined FPR_{max} of 0.15 false predictions per hour. For the "AND" combination (Fig. 2A) and a combination window of 30 min, several alarms of the individual methods were false alarms. Because they were not followed by an alarm of the other method during the combination window, the "AND" combination reduces the number of false alarms considerably. By the "OR" combination, the predictions of both methods are complemented (Fig. 2B). Whereas one seizure was predicted correctly by the MPC and another by

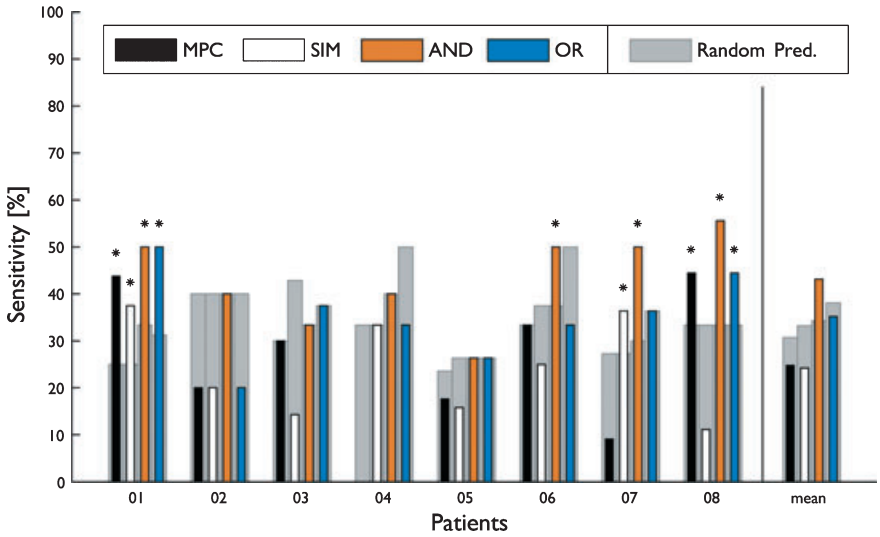

Figure 3.
Results of the optimized combinations following a logical "AND" and "OR," in comparison to the results of the individual methods mean phase coherence (MPC) and dynamic similarity index (SIM). Seizure occurrence period (SOP) duration was set to 30 min, FPR_{max} to 0.15 false alarms per hour, and the intervention time (IT) was optimized for each patient to a duration of between 10 and 60 min. For the "AND" combination, a combination window of 30 min was used. Significant sensitivity values that exceed the corresponding sensitivities of the random predictor (light gray in the background) in a patient are marked by an asterisk. Sensitivity in this group averages 24.8% for the MPC, and 24.2% for the SIM. For the "AND" combination, average sensitivities of 43.2%, and 35.2% for the "OR" combination are observed.

Table 3. Patient individual optimal intervention times

Patient	1	2	3	4	5	6	7	8
MPC	10	40	10	10	20	50	40	40
SIM	10	50	50	20	10	10	40	10
"AND" Comb.	40	30	20	40	10	10	50	30
"OR" Comb.	10	40	40	20	10	50	40	40

Intervention time (IT) in minutes for the mean phase coherence (MPC), the dynamic similarity index (SIM), and the "AND" and "OR" combination for a seizure occurrence period (SOP) of 30 min, a combination window of 30 min, and a maximum false prediction rate of 0.15 false predictions per hour.

the SIM, it is able to correctly predict two of four seizures—while still maintaining FPR_{max}.

Performance of individual and combined prediction methods

Observed prediction sensitivities are displayed together with the sensitivities of the random predictor for all eight patients in Fig. 3 (cf. Table 3 for optimal IT values). Based on individual methods, two patients showed a significant prediction performance for the MPC, with an average sensitivity of 24.8%, and two patients for the SIM, with an average sensitivity of 24.2%. Given identical predefined maximum false predictions rates, the "AND" combination results in significant results for four patients for a combination window of 30 min, with an average sensitivity of 43.2%. The results can be considered significant for the whole group if they exceed the sensitivity of the random predictor for three or more patients (cf. Supporting Information), which is the case for the "AND" combination. For the "OR" combination, significant results can be observed only for two patients, with an average sensitivity of 35.2%.

Sensitivities achieved by the "AND" combination were higher in all eight patients compared to the performance of the individual methods. On average for all patients, the sensitivity of the "AND" combination exceeds the sensitivity of the random predictor. This corresponds to the observation of higher or at least equal sensitivity of the "AND" combination in all patients compared to the random predictor.

In a further analysis, different seizure types (simple partial, complex partial, and generalized tonic–clonic) were analyzed with regard to possible differences in prediction performance. For the eight patients studied here, in whom the dominant seizure type was variable, no significant differences were found.

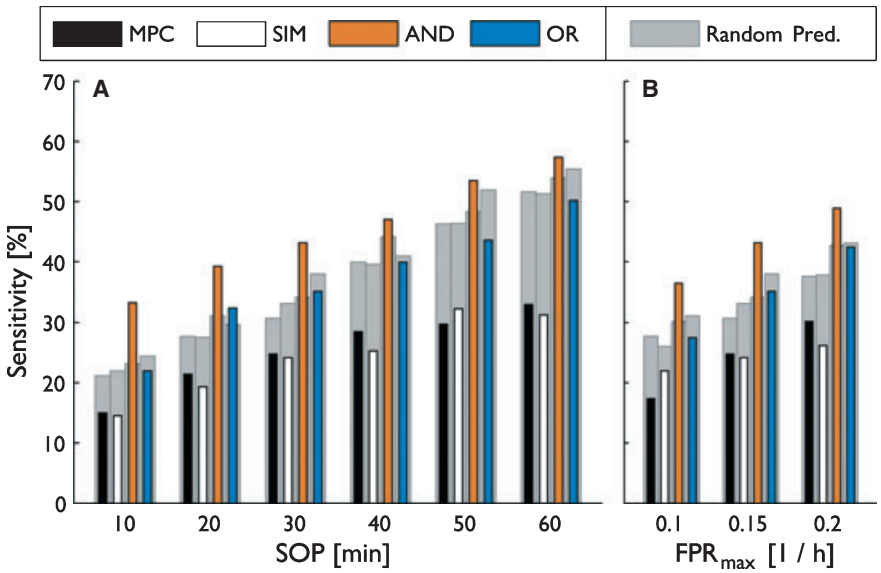

Figure 4.
Average prediction sensitivities for all patients based on the mean phase coherence (MPC), the dynamic similarity index (SIM), and the "AND" and the "OR" combination together with average sensitivities of the random predictor, depending on the duration of the seizure occurrence period (SOP) and on the maximum false prediction rate FPR_{max}. For the "AND" combination, a combination window of 30 min was used. (**A**) Increase in sensitivities with duration of SOP for a fixed FPR_{max} of 0.15 false predictions per hour. (**B**) Increase in sensitivities with maximum false prediction rate FPR_{max} for a fixed SOP of 30 min. For each patient and prediction method, intervention time (IT) was optimized to a value between 10 and 60 min. The superiority of both "AND" and "OR" combinations is stable over the parameter range assessed. For the "AND" combination, observed sensitivities exceed the sensitivity of the random predictor consistently for the average of all patients.

Dependencies on SOP and FPR_{max}

To assess the robustness of the results obtained, prediction performances of both individual prediction methods and their combinations were analyzed for several predefined SOPs and false prediction rates. For a fixed FPR_{max} of 0.15 false predictions per hour, increasing durations of SOP run parallel with an increase in prediction sensitivity (Fig. 4A). With SOPs of 10–60 min, the improvements of the ''AND'' combinations are stable; the increase in sensitivity ranges on average for all patients from a factor 1.65 (for an SOP of 40 min) to 2.2 (for an SOP of 10 min) in comparison to the sensitivity of the best individual method. Similarly, sensitivities are improved by the ''OR'' combinations ranging from a factor of 1.35 (for an SOP of 50 min) to 1.52 (for an SOP of 60 min).

When FPR_{max} is varied for a fixed SOP of 30 min (Fig. 4B), sensitivities are improved by the ''AND'' combination by a factor of 1.62 (for an FPR_{max} of 0.2/h) to 1.74 (for an FPR_{max} of 0.15/h). For the ''OR'' combination, the sensitivities increase by a factor of 1.25 (for an FPR_{max} of 0.1/h) to 1.42 (for an FPR_{max} of 0.15/h). The sensitivities of the combined methods for FPR_{max} = 0.1 false predictions per hour lie in the range of the sensitivities of the individual prediction methods observed for FPR_{max} of 0.2 false predictions per hour.

The number of patients with significant prediction performances was stable when SOP and FPR_{max} were varied. Again, only for the ''AND'' combination sensitivities on average were higher than those of the random predictor.

Discussion

Precursors of imminent epileptic seizures have been reported in a number of studies using a variety of features derived from EEG recordings. Whereas some of these have a statistically significant predictive value, their performance currently remains insufficient for clinical applications (Ebersole, 2005; Mormann et al., 2006; Schelter et al., 2007). This is due to an unfavorable relationship between achieved sensitivity and specificity.

This study for the first time systematically investigates the possibility of combining different seizure prediction algorithms to improve prediction performances. The analysis is based on a database with continuous long-term recordings of intracranial EEG, lasting on average 182 h and including on average 19.1 seizures per patient. The algorithms analyzed were found to reflect different aspects of brain dynamics corresponding to different points in time when alarms are triggered. We could show that sensitivity

can be increased for the combination of the univariate SIM and the bivariate MPC, given a fixed maximum false prediction rate.

Using the logical ''AND'' combination, for which both methods must trigger individual alarms during a specified time window to trigger an alarm of the combined system, the number of patients showing significant prediction performance doubled from two to four of eight patients for an SOP of 30 min and an FPR_{max} of 0.15 false predictions per hour. In comparison to the random predictor, this represents a significant prediction performance for the whole group of patients for the ''AND'' combination. Moreover, the average sensitivity was increased by a factor of 1.79. For the patients analyzed here, the ''OR'' combination, for which each single alarm of one method leads to an alarm of the combined system, had a smaller effect but also increased sensitivities by a factor of 1.46 on average. Because the performance increase of the ''AND'' combination is higher than that of the ''OR'' combination, it can be concluded that the correct alarms of the individual methods investigated here are more highly correlated than the false alarms. We could further show that these improvements were robust over a range of reasonable SOPs and at various predefined maximum false prediction rates. Depending on clinical needs, it is thus not only possible to increase sensitivity. The focus of improvement can also be laid on reducing the rate of false predictions in comparison to individual methods.

These findings demonstrate that different aspects of changes in preictal dynamics can be combined in an advantageous manner, and characteristics of various methods can be joined. Using the Boolean operations introduced here, two scenarios are conceivable: if, on the one hand, the applied individual prediction methods are known to produce independently occurring false alarms, the ''AND'' combination is a promising approach to reduce the number of false alarms considerably. On the other hand, if prediction methods are available that complement each other with respect to correct predictions, the ''OR'' combination may offer advantages by joining the predictive power of the individual methods. With regard to future clinical applications, both approaches can be advantageous, depending on the severity of side effects of the interventions.

The optimized combination of prediction methods introduced in this study allows an adaptation of the combined methods to these requirements. For intervention systems with minor side effects like pharmaceutical or electrical intervention at the focus site, it can be optimized for the desired high sensitivities, since false alarms are of less importance in these scenarios. If alarms are issued to warn the patient, however, optimal specificity must be achieved, such that the patient is not impaired by many false predictions. By applying the paradigm of optimized combination, either can be accomplished. For the future, based on the results presented, investigations of more complex strategies like weighted combinations instead of the Boolean ''AND'' or ''OR'' may be promising and could contribute to a further increase in prediction sensitivity.

In addition, the systematic analysis of different prediction methods could serve for the rational selection of methods that provide complementary aspects of preictal EEG dynamics. As a second step, it is conceivable to tune prediction methods to focus on a certain aspect of brain dynamics with high sensitivities not covered by others.

The proof of principle given by this study opens up a window for new ways to combine prediction methods that were used individually during the last decade (Mormann et al., 2007). Given the markedly improved sensitivities at fixed maximum false prediction rates, this represents a relevant step toward applications in clinical settings.

Acknowledgments

We would like to thank Carolin Gierschner and the team of EEG technicians at the Freiburg Epilepsy Center for their technical support, especially concerning the extensive data acquisition and handling. This work was supported by the German Federal Ministry of Education and Research (BMBF grant 01GQ0420), the Excellence Initiative of the German Federal and State Governments, the European Union (Grant 211713), and the German Science Foundation (Ti 315/4-2; Sonderforschungsbereich-TR3; He1949/1-1).

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with this guideline.

Disclosure

None of the authors has any conflict of interest to disclose.

References

Ebersole JS. (2005) In search of seizure prediction: a critique. *J Clin Neurophysiol* 116:489–492.

Engel J, Rasmussen TB. (1993) Outcome with respect to seizures. In Engel J (Ed) *Surgical treatment of epilepsies*. Raven Press, New York, pp. 609–621.

Esteller R, Echauz J, D'Alessandro M, Worrell G, Cranstoun S, Vachtsevanos G, Litt B. (2005) Continuous energy variation during the seizure cycle: towards an on-line accumulated energy. *Clin Neurophysiol* 116:517–526.

Hauser WA, Annegers JF, Rocca WA. (1996) Descriptive epidemiology of epilepsy: contributions of population-based studies from Rochester, Minnesota. *Mayo Clin Proc* 71:576–586.

Haut SR, Swick C, Freeman K, Spencer S. (2002) Seizure clustering during epilepsy monitoring. *Epilepsia* 43:711–715.

Iasemidis LD, Pardalos P, Sackellares JC, Shiau DS. (2001) Quadratic binary programming and dynamical system approach to determine the predictability of epileptic seizures. *J Comb Optim* 5:9–26.

Iasemidis LD, Shiau DS, Pardalos PM, Chaovalitwongse W, Narayanan K, Prasad A, Tsakalis K, Carney P, Sackellares J. (2005) Long-term prospective on-line real-time seizure prediction. *Clin Neurophysiol* 116:532–544.

Kalitzin S, Velis D, Suffczynski P, Parra J, Lopes da Silva F. (2005) Electrical brain-stimulation paradigm for estimating the seizure onset site and the time to ictal transition in temporal lobe epilepsy. *Clin Neurophysiol* 116:718–728.

Le van Quyen M, Martinerie J, Baulac M, Varela F. (1999) Anticipating epileptic seizures in real time by a non-linear analysis of similarity between EEG recordings. *Neuroreport* 10:2149–2155.

Le van Quyen M, Adam C, Martinerie J, Baulac M, Clemenceau S, Varela F. (2000) Spatio-temporal characterizations of non-linear changes in intracranial activities prior to human temporal lobe seizures. *Eur J Neurosci* 12:2124–2134.

Le van Quyen M, Martinerie J, Navarro V, Baulac M, Varela F. (2001a) Characterizing neurodynamic changes before seizures. *J Clin Neurophysiol* 18:191–208.

Le van Quyen M, Martinerie J, Navarro V, Boon P, D'Have M, Adam C, Renault B, Varela F, Baulac M. (2001b) Anticipation of epileptic seizures from standard EEG recordings. *Lancet* 357:183–188.

Le van Quyen M, Soss J, Navarro V, Robertson R, Chavez M, Baulac M, Martinerie J. (2005) Preictal state identification by synchronization changes in long-term intracranial EEG recordings. *J Clin Neurophysiol* 116:559–568.

Lehnertz K, Elger CE. (1998) Can epileptic seizures be predicted? Evidence from nonlinear time series analysis of brain electrical activity. *Phys Rev Lett* 80:5019–5023.

Li Y, Mogul DJ. (2007) Electrical control of epileptic seizures. *J Clin Neurophysiol* 24:197–204.

Litt B, Esteller R, Echauz J, D'Alessandro M, Shor R, Henry T, Pennell P, Epstein C, Bakay R, Dichter M, Vachtsevanos G. (2001) Epileptic seizures may begin hours in advance of clinical onset: a report of five patients. *Neuron* 30:51–64.

Lopes da Silva FH, Blanes W, Kalitzin SN, Parra J, Suffczynski P, Velis DN. (2003a) Dynamical diseases of brain systems: different routes to epileptic seizures. *IEEE Trans Biomed Eng* 50:540–548.

Lopes da Silva F, Blanes W, Kalitzin SN, Parra J, Suffczynski P, Velis DN. (2003b) Epilepsies as dynamical diseases of brain systems: basic models of the transition between normal and epileptic activity. *Epilepsia* 44:72–83.

Martinerie J, Adam C, Le Van Quyen M, Baulac M, Clemenceau S, Renault B, Varela F. (1998) Epileptic seizures can be anticipated by non-linear analysis. *Nat Med* 4:1173–1176.

Mormann F, Lehnertz K, David P, Elger CE. (2000) Mean phase coherence as a measure for phase synchronization and its application to the EEG of epilepsy patients. *Physica D* 144:358–369.

Mormann F, Andrzejak RG, Kreuz T, Rieke C, David P, Elger CE, Lehnertz K. (2003a) Automated detection of a pre-seizure state based on a decrease in synchronization in intracranial EEG recordings from epilepsy patients. *Phys Rev E* 67:021912.

Mormann F, Kreuz T, Andrzejak R, David P, Lehnertz K, Elger CE. (2003b) Epileptic seizures are preceded by a decrease in synchronization. *Epilepsy Res* 53:173–185.

Mormann F, Kreuz T, Rieke C, Andrzejak RG, Kraskov A, David P, Elger CE, Lehnertz K. (2005) On the predictability of epileptic seizures. *J Clin Neurophysiol* 116:569–587.

Mormann F, Elger CE, Lehnertz K. (2006) Seizure anticipation: from algorithms to clinical practice. *Curr Opin Neurol* 19:187–193.

Mormann F, Andrzejak RG, Elger CE, Lehnertz K. (2007) Seizure prediction: the long and winding road. *Brain* 130:314–333.

Navarro V, Martinerie J, Le Van Quyen M, Clemenceau S, Adam C, Baulac M, Varela F. (2002) Seizure anticipation in human neocortical partial epilepsy. *Brain* 125:640–655.

Navarro V, Martinerie J, Le Van Quyen M, Baulac M, Dubeau F, Gotman J. (2005) Seizure anticipation: do mathematical measures correlate with video-EEG evaluation? *Epilepsia* 46:385–396.

Rosenblum MG, Pikovsky AS, Kurths J. (1996) Phase synchronization of chaotic oscillators. *Phys Rev Lett* 76:1804–1807.

Sackellares JC. (2008) Seizure prediction. *Epilepsy Curr* 8:55–59.

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

Schelter B, Winterhalder M, Maiwald T, Brandt A, Schad A, Timmer J, Schulze-Bonhage A. (2006b) Do false predictions of seizures depend on the state of vigilance? A report from two seizure prediction methods and proposed remedies. *Epilepsia* 7:2058–2070.

Schelter B, Winterhalder M, Feldwisch genannt Drentrup H, Wohlmuth J, Nawrath J, Brandt A, Schulze-Bonhage A, Timmer J. (2007) Seizure prediction: the impact of long prediction horizons. *Epilepsy Res* 73:213–217.

Schindler K, Wiest R, Kollar M, Donati F. (2002) EEG analysis with simulated neuronal cell models helps to detect pre-seizure changes. *Clin Neurophysiol* 113:604–614.

Stein AG, Eder HG, Blum DE, Drachev A, Fisher RS. (2000) An automated drug delivery system for focal epilepsy. *Epilepsy Res* 39:103–114.

Winterhalder M, Maiwald T, Voss HU, 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.

Winterhalder M, Schelter B, Maiwald T, Brandt A, Schad A, Schulze-Bonhage A, Timmer J. (2006) Spatio-temporal patient-individual assessment of synchronization changes for epileptic seizure prediction. *J Clin Neurophysiol* 117:2399–2413.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Methods S1. Detailed information about the individual prediction methods used; derivation of the analytical random predictor.

Please note: Wiley-Blackwell is not responsible for the content or functionality of any supporting information supplied by the authors. Any queries (other than missing material) should be directed to the corresponding author for the article.