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SPECIAL REPORT

The EPILEPSIAE database: An extensive electroencephalography database of epilepsy patients

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Summary

From the very beginning the seizure prediction community faced problems concerning evaluation, standardization, and reproducibility of its studies. One of the main reasons for these shortcomings was the lack of access to high-quality long-term electroencephalography (EEG) data. In this article we present the EPILEPSIAE database, which was made publicly available in 2012. We illustrate its content and scope. The EPILEPSIAE database provides long-term EEG recordings of 275 patients as well as extensive metadata and standardized annotation of the data sets. It will adhere to the current standards in the field of prediction and facilitate reproducibility and comparison of those studies. Beyond seizure prediction, it may also be of considerable benefit for studies focusing on seizure detection, basic neurophysiology, and other fields.

KEY WORDS: Seizure prediction, Presurgical monitoring, Electroencephalogram, ECoG, Neurophysiological database.

More than 0.5% of the world's population has epilepsy. During the suddenly occurring seizures that characterize this neurologic disorder, patients may undergo loss of consciousness and/or motor control and therefore are severely restricted in daily life (Schulze-Bonhage & Buller, 2008). Seizure control may be achieved by antiepileptic drugs or surgery for only two thirds of all epilepsy patients. For the remaining one third, new treatment strategies are of crucial importance. One promising approach is the prediction of seizures. If it was possible to reliably predict seizure onsets, interventions could be applied in a closed-loop manner (Stacey & Litt, 2008). This would allow timely targeted seizure-suppressive medication (Stein et al., 2000) or electrical stimulation right before a seizure in order to prevent it (Theodore & Fisher, 2004; Osorio et al., 2005; Morrell, 2006; Sunderam et al., 2010).

Since the 1980s, much effort has been invested to identify precursors of seizures in electroencephalography (EEG) (Mormann et al., 2007; Schelter et al., 2008). Because no reliable precursors were found by mere visual inspection, mathematical analysis of EEG was employed to reveal more complex changes in neural activity preceding seizures. Linear (Rogowski et al., 1981; Salant et al., 1998) as well as nonlinear (Iasemidis et al., 1990; Lehnertz & Elger, 1995; Martinerie et al., 1998; Le Van Quyen et al., 1999, 2005; Mormann et al., 2007; Stacey et al., 2011; Teixeira et al., 2011) approaches were applied. Recently, also the electrocardiography (ECG) was analyzed to complement EEG (Delamont et al., 1999; Kerem & Geva, 2005; Valderrama et al., 2010).

However, most early studies were biased in several ways. They included only selected preictal data and contained only small numbers of patients as well as seizures. This led to many shortcomings as, for example, the inability to determine the specificity of prediction algorithms applied to interictal data, and also to overfitting. If only preictal data is

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used to evaluate a predictive algorithm one may only access its sensitivity. It is possible, though, that alarms are raised based on EEG patterns that often occur during interictal periods, as well. To reveal the poor specificity of such predictors, in addition one must test their performance on interictal data. A recent study showed that the sensitivity of previously published prediction algorithms was negatively correlated with both average recording duration as well as average number of seizures contained therein (Schulze-Bonhage et al., 2011). An ideal study should be based on a continuous long-term data set used for optimizing the prediction system and a second data set from the same patient for evaluating its performance in a quasi-prospective manner. Hence, high-quality long-term EEG recordings of many patients containing interictal data is required. To facilitate reproducibility, publicly available databases are of great benefit.

During the last years, research groups became increasingly aware of the biases mentioned above and as a consequence the first publicly accessible databases were installed. They were provided by the epilepsy centers in Bonn, Germany (http://epileptologie-bonn.de/cms/front_content.php?idcat=193) and Freiburg, Germany (http://epilepsy.uni-freiburg.de/freiburg-seizure-prediction-project/eeg-database), as well as by the Children's Hospital (Boston, MA, U.S.A.: http://www.physionet.org/pn6/chbmit/). All of these databases contain recordings performed during presurgical epilepsy monitoring, that is, the patients underwent long-term recordings of the intracranial EEG (databases from Bonn, Freiburg, and Lawrence), or scalp EEG (database from Boston). The number of patients ranged from 5 to 23, the duration of the recordings from 40 min to 142 h, and total number of seizures from 59 to 189. Although being a first step in the right direction, those databases still contained only small amounts of data and provided little annotations and metadata.

In 2008 the European Union funded project EPILEPSIAE (http://www.epilepsiae.eu/) was started, with six partners from hospitals, universities, and industry in France, Germany, Italy, and Portugal. In the course of this project, the largest epilepsy database worldwide has been compiled, consisting of data sets of 275 patients (http://epilepsy-database.eu/) and exceeding earlier databases by more than an order of magnitude. In addition to the recordings of the EEG and ECG of the patients, it contains extensive metadata on technical and clinical details of the recordings and clinical information about patients. All annotations are based on standardized annotation rules.

In 2012 this database has been made available to the public, allowing researchers worldwide to conduct high-quality studies not only in the field of seizure prediction, but also seizure detection, basic neurophysiology, and other fields. In the following, the precise content of the EPILEPSIAE database is presented as well as some basic characteristics of the data sets. The latter may illustrate the scope of the database and the wide variety of possible queries it offers to researchers. The relational system underlying the database allows users to comfortably search for specific questions and for selection of homogeneous patient groups. The data are accessible via a graphical interface with input masks for selected queries. Furthermore, expert users may conduct any kind of SQL queries. We report distribution of seizures with respect to circadian rhythms, states of vigilance, and progress of the recording, no less than distributions of length of ictal and interictal periods. Differences between clinical and EEG-based seizure onset will be considered as well as the spatial propagation of seizures. All of this will be done for the entire group of patients as well as for subgroups regarding, for example, the type of epilepsy, medication, pathology, outcome of surgical resection, and type of electrodes in order to reveal possible correlations.

Database Content

The database contains recordings and metadata of 275 patients from the epilepsy centers of the University Hospital Freiburg, Germany, of the University Hospital of Coimbra, Portugal, and of the Hopital de la Pitier-Salpetriere in Paris, France. The EEG/ECG data have been registered during long-term presurgical monitoring. During recording, each patient had at least three clinically manifest seizures with interictal intervals of >4 h. Moreover data sets had to fulfill annotation standards defined by the consortium of epilepsy centers collaborating within the EPILEPSIAE project. Recordings of the patients last 165 h on average with maximum durations of 500 h providing >40,000 h of data in total.

Data

The database comprises surface recordings from 217 patients as well as invasive EEG recordings from 58 patients. The number of seizures per patient range from 3 to 94. Surface recordings were performed by a 10–20 electrode scheme, for some patients extended by additional electrode contacts. For patients with invasive recordings, intracranially implanted grids, strips, and/or stereotactically implanted depth electrodes were used, including up to 125 electrode channels for some patients. Sampling rates range from 250 Hz to 2.5 kHz. In the case of intracranial recordings, three-dimensional coordinates of the electrodes according to the Montreal Neurologic Institute (MNI) coordinate system (Evans et al., 1993) are provided for each patient as well as functions for calculating the equally widespread Talairach coordinates (Talairach & Tournoux, 1988). Some patients underwent additional surface recordings during intracranial registrations. For all patients, the electrocardiography (ECG) was also recorded. For 65% of patients, electromyography (EMG) of the submental muscle for sleep staging is stored. All electrophysiologic recordings are stored in a simple binary format with additional header files containing information about the sampling frequency, start, and length of the file.

Clinical annotations

One of the main advantages of the EPILEPSIAE database, setting it apart from all previous databases, is its extended and standardized annotation scheme. Based on both video analysis and EEG screening, for each patient all clinical seizures were annotated by experienced staff members including the time of first visually identified electrographic and clinical changes, and both electrographic and clinical seizure onset and offset. Seizures are categorized according to their dominant pattern, to their type, for example, simple, complex partial, or secondarily generalized, as well as the state of vigilance 10 s before seizure onset. The spatial propagation of seizure activity is provided by specifying the electrode contacts involved in initial seizure activity, early propagation, as well as late propagation. For the majority of seizures, detailed information about the semiology is given. In addition to clinically manifest seizures, for patients for whom also subclinical seizures occurred, the time of occurrence of the first subclinical seizures is included. Beyond the annotations of seizures, interictal events like typical spike patterns or abnormal EEG activity are marked.

Metadata

Along with the annotated EEG and ECG data, extensive metadata are stored in the EPILEPSIAE database, which ranges from the patient's age and the recording hospital to neurologic findings and MR images. Information on each patient's epilepsy characteristics such as etiology, neuropsychological data, and seizure frequency is provided. Furthermore, details concerning antiepileptic medication during the monitoring may be inferred. Regarding data acquisition, the type of electrodes, and, in the case of invasive recordings, the date of implantation is given. Because the long-term monitoring of all the patients was performed for the purpose of presurgical evaluation, decisions on subsequent surgery and its outcome are also provided. Figure 1 shows a summary of basic demographic and clinical data of the patients in the EPILEPSIAE database.

Data Characteristics

In order to predict seizures it is helpful to acquire knowledge regarding their distribution in time, duration, and spatial propagation as well as potential correlations between those characteristics and, for example, the type of epilepsy. Questions about seizure distribution were already addressed previously, yet often only on short-term and/or discontinuous EEG data or as in Milton et al., 1987 only based on patient's seizure diaries. Small numbers of seizures diminish statistical relevance of the results obtained. Although recent studies were also based on larger data sets and long-term EEG data, a peculiarity of the recordings in the EPILEPSIAE database is the presurgical setting in which they were acquired. During presurgical monitoring there is only little antiepileptic medication, and often intracranial electrodes are used. Given the extensive pool of EEG/ECG data on epilepsy patients accumulated, the questions mentioned above may be addressed once again in a manner that allows for statistically reliable results.

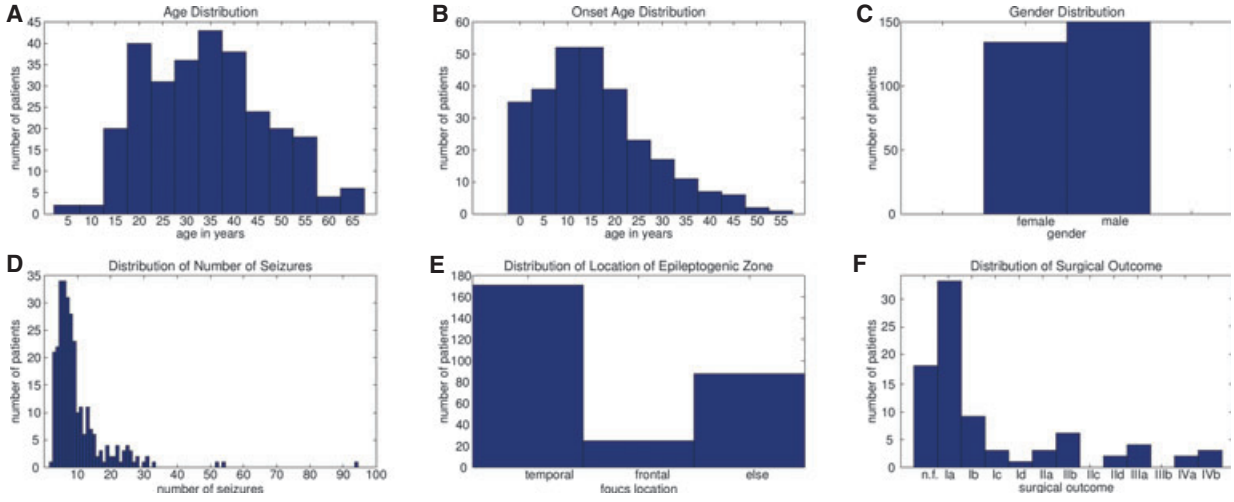

Figure 1.

(**A**) Age distribution of all patients. (**B**) Onset age distribution of all patients. (**C**) Gender distribution of all patients. (**D**) Distribution of number of seizures per patient. (**E**) Overview of epileptogenic foci location of all patients. (**F**) Overview of surgical outcome from 84 patients who underwent epilepsy surgery. 1: n.f., no follow-up; Ia–IVb, Engel classification.

Distribution of seizures during the course of recordings

In the following we describe the distribution of seizures in the EPILEPSIAE database with respect to the recording, circadian rhythms, and states of vigilance. The results are based on data of 275 patients with an average of 9.68 seizures per patient. This by far exceeds the size of databases used in previous studies (Schulze-Bonhage et al., 2011). The average distribution of seizures during the recording is depicted in Fig. 2. The last bin of the histogram shown is highly biased. Recordings were discontinued when a sufficient number of seizures was reached. Therefore, they tend to end with postictal rather than interictal data, which leads to an exaggeration of the last bin. Despite this bias one may clearly see an increased seizure rate toward the end of the recording. By comparing the seizure rate during the course of the recording with the average drug level, one may deduce that the decreasing dose of antiepileptic medication causes this effect. The shape of the drug level curve is well reflected by the course of seizure rates along the recording, especially if one does not take into account the last bin.

In the field of seizure prediction it is a common strategy to preselect one or more possibly predictive features (i.e., time series derived from the EEG), to optimize a threshold, and to trigger an alarm in case the feature crosses this threshold (Mormann et al., 2007; Feldwisch-Drentrup et al., 2010, 2011). If parameters are optimized on a training data set, changing medication levels may hamper the application of prediction methods. Due to decreasing drug level and therefore increasing seizure rate in the course of the training epoch, the predictor might be optimized such that it slowly drifts in time. And it will do so even if medication and seizure rate are stable across the test data, which it is applied to afterward. Therefore the obtained feature does not represent the factual seizure risk. Hence it is crucial to ensure that prediction features are not optimized such that they reflect the patient's drug level rather than his or her factual seizure probability.

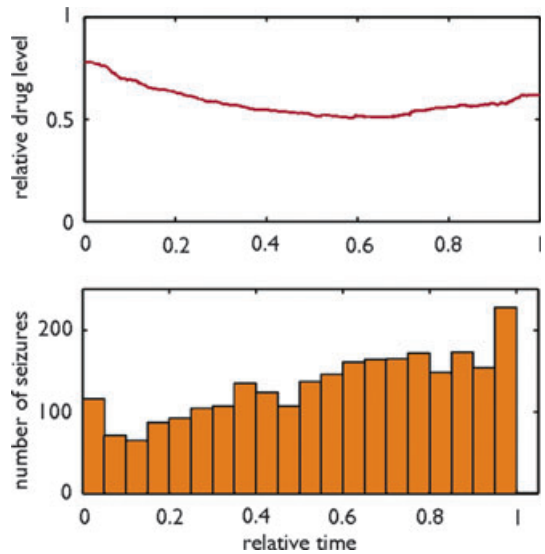

Figure 2.
Medication level during the recording (upper row) and distribution of seizures with respect to recording progress (lower row), averaged over all 275 patients. Different drugs were weighted equally. The individual drug level reaches the maximum value of one if the patient's personal maximum dose of each drug is administered. Time was scaled to the overall recording length of each patient. The histogram shows the number of seizures taking place during the first 5% of the recording, the second 5%, and so on.

Distribution of seizures with respect to time of the day

Circadian rhythms in the occurrence of epileptic seizures were observed early in epilepsy research, and led to classifications in ''diurnal,'' ''nocturnal,'' and ''diffuse'' seizures (Gowers, 1885; Langdon-Down & Brain, 1929; Grifiths & Fox, 1938). In subsequent studies it was found that seizure distributions in patients with medial temporal lobe epilepsy (MTLE) often show a primary peak in seizure occurrence in the late afternoon, and a secondary peak in the morning, whereas patients with frontal lobe epilepsy (FLE) tend to have seizures mostly in the early morning (Durazzo et al., 2008).

Figure 3 shows histograms of seizure occurrence plotted against time of the day. In accordance with the literature, peaks can be observed in seizure occurrence both in the early morning and the late afternoon. In addition, Fig. 3 also presents the sleep stages of the patients 10 s before seizure onsets. As observed previously (Quigg et al., 1998), most seizures that occur during the night start during light sleep (stages I and II), few during deep sleep (stages III and IV), and almost none during rapid eye movement (REM) sleep. In total, 61.6% of all seizures occurs when the patient is awake, 4.3% during sleep stage I, 21.5% during sleep stage II, 1.6% during sleep stage III, 0.4% during sleep stage IV, and 1.9% during REM sleep. For patients undergoing invasive recordings without any scalp electrodes, sleep staging of the EEG cannot be performed. Hence, these seizures remain unclassified (8.6% of all seizures).

Duration of ictal and interictal periods

The duration of ictal and interictal periods may yield information regarding the clustering of seizures as well as the dynamics governing transitions from ictal to interictal states and vice versa. Distributions of the average durations of ictal and interictal periods are shown in Figs 4 and 5, respectively. The histograms were fitted with a Γ-distribution

$$\frac{1}{N} x^{a-1} e^{\frac{-x}{b}}$$

where N serves normalization and a is the so-called shape parameter. If a = 1, the Γ-distribution yields an

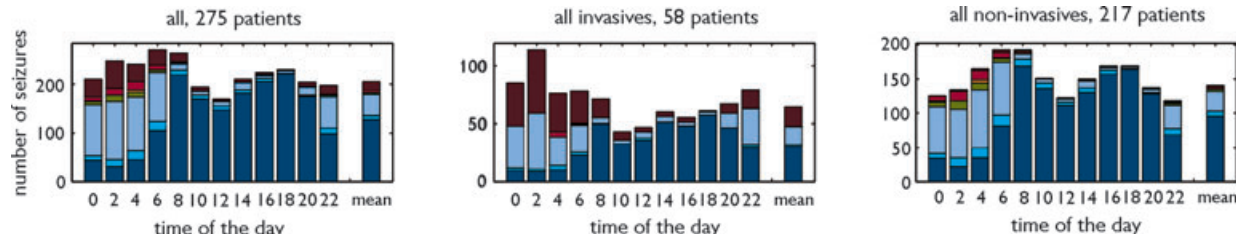

Figure 3.
Distribution of seizures with respect to circadian rhythm and states of vigilance. Numbers are averaged over all patients belonging to the indicated subgroup. Seizures occurred either during the awake state (dark blue), during sleep stage I (medium blue), during sleep stage II (light blue), during sleep stage III (green), during sleep stage IV (orange), during REM sleep (light red), or are unclassified (dark red).
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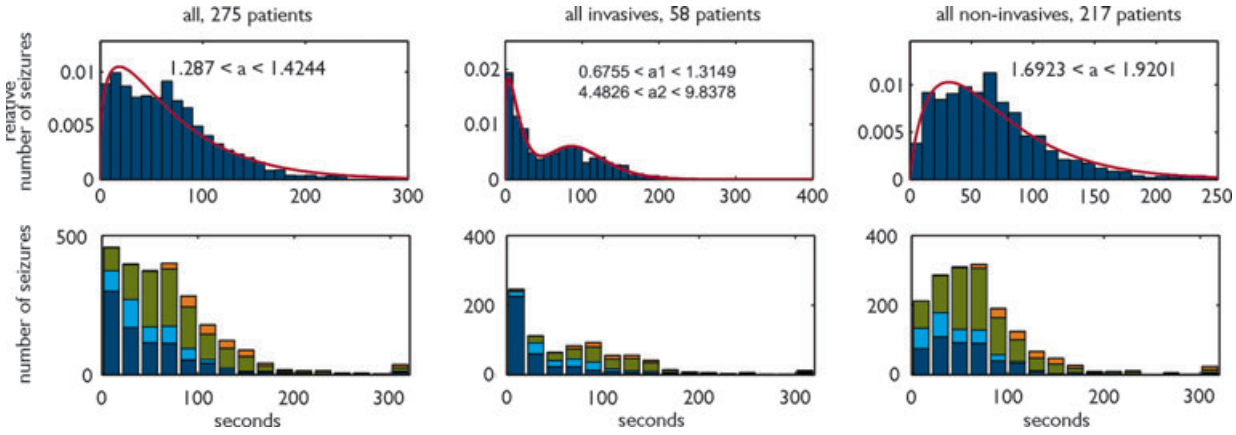

Figure 4.
Distribution of duration of seizures. The red line in the upper row is a fitted Γ-distribution with shape parameter a. The 95% confidence intervals for a are given. The lower row reveals the single contributions of the different seizure types: dark blue = simple, light blue = not classified, light green = complex partial, orange = secondarily generalized. Numbers are averaged over all patients belonging to the indicated subgroup.
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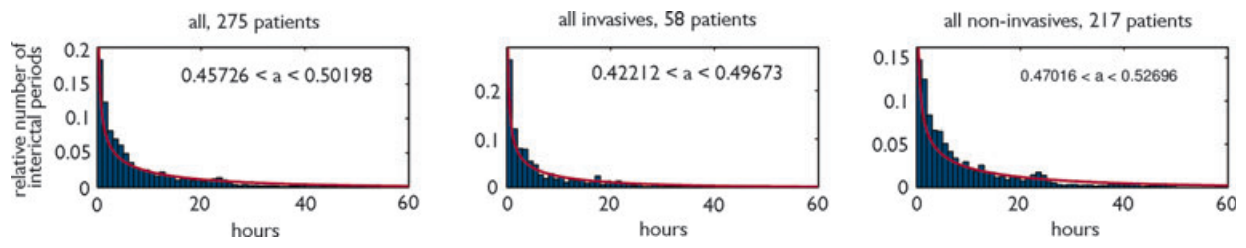

Figure 5.
Distribution of durations of interictal periods. The red line is a fitted Γ-distribution with shape parameter a. The 95% confidence intervals for a are given. Numbers are averaged over all patients belonging to the indicated subgroup.
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exponential distribution, thus indicating a Poisson process underlying the dynamics under consideration (Doob, 1990). In Poisson processes, events occur with equal probability rate in any given time interval. On the contrary, if a is smaller than 1 the chance of an event to happen decreases with time and if a is >1 it increases. In the latter case, the Γ-distribution shows a maximum at a finite value indicating a preferred duration of interevent

periods and thus implying a periodic process to govern event occurrence.

The 95% confidence intervals for the shape parameter a are given in Figs 3 and 4. The distribution of seizure durations clearly shows a superposition of two distinct distributions. Accordingly we used as a fit function a superposition of two Γ-distribution instead of only one and therefore obtained two shape parameters: a1 and a2. Considering the single contributions of the different seizure types shown in the lower row of Fig. 4, it becomes obvious that higher durations relate to complex partial and secondarily generalized seizures, whereas smaller durations relate to simple and not classified seizures. The significantly differing duration of complex partial seizures was reported before and is confirmed by our analysis. Those durations show a distinct maximum at a finite value (90 s), which is reflected by the 95% confidence interval $4.483 < a2 < 9.838$ of the corresponding shape parameter being above the value one. Therefore the null hypothesis of the termination of complex partial seizures being a Poisson process may unequivocally be rejected. Rather than being equally probable at any given point in time during complex partial seizures, the chance for termination grows within the ongoing ictal period.

The durations of interictal periods shown in Fig. 5 exhibit 95% confidence intervals of shape parameter a much below one. This is incompatible with a Poisson process determining seizure onset times. The chance for a seizure to occur decreases within the ongoing interictal period. The longer the patient has gone without seizures, the less likely is a new onset. In other words: seizures beget seizures (Hauser & Lee, 2002). Compared to seizures detected in the scalp EEG, invasively recorded ones are separated by rather short interictal periods. This may indicate higher clustering of those seizures, or the diminished interictal duration may simply result from intracranial electrodes that lie closer to the epileptic focus and therefore detect more seizures in general. This necessarily leads to shorter interictal periods.

Clinical versus EEG based onset

Because both EEG based and clinical onset are provided for any seizure in the database, one may examine the offset between them. Clinical onsets were determined by video analysis of the patient's behavior, whereas the EEG-based onsets where determined by visual inspection of the EEG by experienced staff members. Figure 6 shows the distributions of the such determined time lags, where positive values correspond to a preceding EEG-based onset. For intracranially recorded seizures the average advance of the EEG-based onset is significantly larger than 0. This seems to be intuitive, since invasive electrodes are closer to the spatial origin of seizures.

Propagation

For all seizures contained in the EPILEPSIAE database, information on spatial propagation is provided. This information comprises the number of electrodes involved during seizure initiation, the early propagation (within 10 s), and the late propagation. Figure 7 shows averaged propagation schemes. The spreading of temporal lobe seizures clearly differs from that of frontal lobe seizures. Whereas seizures of frontal lobe type reach their maximum number of involved electrodes rather quickly, seizures of temporal lobe type continue spreading also toward the end of an ictal period. Furthermore, the maximum number of involved electrodes of frontal lobe seizures is significantly higher than that of temporal lobe seizures. The latter may be due to more limited spread in temporal lobe seizures, but may also reflect different implantation schemes used for frontal lobe and temporal lobe exploration.

Discussion

Up until now, the seizure prediction community worldwide was facing several obstacles hampering its research. Only few research groups had access to EEG data. The data used were often short and/or noncontinuous, and underlying groups of patients were often small. This led to overfitting and little statistical reliability of the results obtained. Moreover, due to missing standards, studies were hardly comparable and reproducibility was not always ensured. To conduct high-quality prediction studies, standardized long-term EEG recordings of many patients containing interictal data are

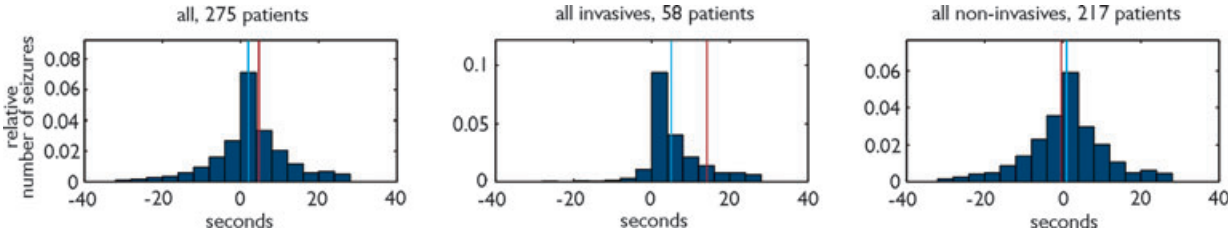

Figure 6.
Difference between EEG-based and clinical onset. Positive values correspond to preceding EEG-based onset. The light blue line indicates the median, whereas the red line is located at the mean of the distribution. Numbers are averaged over all patients belonging to the indicated subgroup.

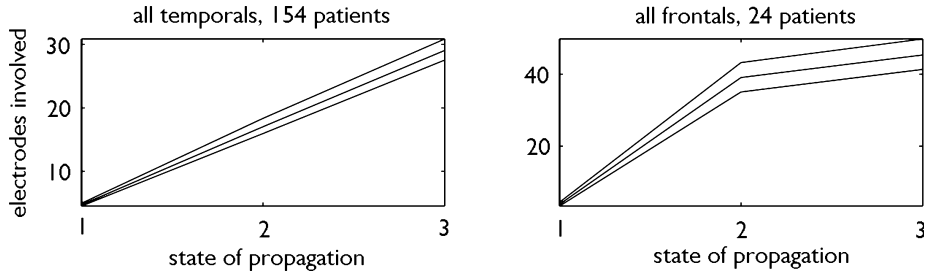

Figure 7.
Spatial seizure development. The y-axis indicates the number of electrodes involved in the origin (1), early state (2), and late state (3) of seizures. Early state is defined as 10 s after seizure onset. Lower and upper limits are 95% confidence intervals obtained by bootstrapping. Numbers are averaged over all patients belonging to the indicated subgroup.
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required. Therefore, data may be split into a continuous long-term dataset used for optimizing the prediction system and a second dataset for evaluating its performance in a quasi-prospective manner.

In the course of the EU-funded EPILEPSIAE project, the largest epilepsy database worldwide has been compiled. Consisting of datasets of 275 patients and comprising 2,662 seizures, it exceeds earlier databases by more than one order of magnitude. In addition to the standardized annotated recordings of the EEG and ECG of the patients, it contains extensive metadata on technical and clinical details of the recordings and clinical information about patients. The scope and content of this database, which will be publicly available in 2012 (conditions listed at epilepsy-database.eu), has been shown in this article. It solves the problem of public availability of well-annotated continuous long-term EEG/ECG data. And it will allow for annotation standards and facilitate reproducibility and comparison of prediction studies as well as studies focusing on seizure detection, basic neurophysiology, and other fields.

The data included were limited to those from patients who were undergoing presurgical monitoring, as these patients are pharmacoresistant and were of particular relevance for applications of seizure prediction as targeted in the EU project EPILEPSIAE. Certainly this criterion as well as the required seizure frequency led to a strong selection bias, and data are not representative of all patients with focal epilepsy. In principle, the database is open to a future extension to other EEG data from patients with a variety of syndromes and investigated for other diagnostic reasons.

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Disclosure

None of the authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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Appendix: Annotation Standard

Seizures

1 Unequivocal clinical seizure onset: first clear-cut subjective symptoms or objective signs related to an ongoing epileptic seizure (e.g., push-button event, seizure-related movement, impaired responsiveness).

2 First behavioral alteration: unspecific, but possible seizure-related changes in behavior preceding (1), for example, awakening from sleep, cessation of prior activity.

3 Unequivocal electroencephalographic seizure onset: onset of clear-cut seizure pattern (defined as a pattern of rhythmic activity, repetitive spiking or amplitude depression with evolution in morphology, spatial extension and/or frequency).

4 First electroencephalographic change, possibly seizure-related but with questionable specificity (e.g., diffuse attenuation of background activity, brief rhythmic patterns without clear evolution):

Seizures with clear epileptic semiology are included in the data analysis also if EEG patterns are not visible either due to lack of spread to the lateral convexity or to muscle artifacts.

Heart rate changes obtained by ECG will be regarded as a (first) clinical sign of a vegetative seizure if there is a clear and stable baseline without changes in vigilance, absence of changes in motor activity, increase or decrease in seizure frequency by more than two standard deviations from the preceding baseline

Similarly, EMG recordings showing typical muscle contractions without movements visible on the video will be regarded as clinical signs.

In cortical dysplasia, only unequivocal seizure patterns will be regarded as ictal events.

For patients with hippocampal sclerosis showing repetitive spiking, seizure onset was set to the point of transition from irregular interictal spiking to the period of repetitive spiking. Furthermore, the evolution into a clear seizure pattern (e.g., spiking of increasing frequency, spread, low amplitude fast activity) is marked.

Subclinical electroencephalographic events

Subclinical seizures were defined as electrographic seizures without observed subjective or objective neurologic or somatic manifestation. The electrographic seizure onset of subclinical seizures was defined as the time of onset of a clear-cut seizure pattern, being a pattern of rhythmic activity, repetitive spiking, or amplitude depression with evolution in morphology, spatial extension, and/or frequency. For each patient, the first 10 subclinical events were marked for each day.