

Epileptic seizures are preceded by a decrease in synchronization

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Abstract

The exact mechanisms leading to the occurrence of epileptic seizures in humans are still poorly understood. It is widely accepted, however, that the process of seizure generation is closely associated with an abnormal synchronization of neurons. In order to investigate this process, we here measure phase synchronization between different regions of the brain using intracranial EEG recordings. Based on our preliminary finding of a preictal drop in synchronization, we investigate whether this phenomenon can be used as a sensitive and specific criterion to characterize a pre-seizure state and to distinguish this state from the interictal interval.

Applying an automated technique for detecting decreased synchronization to EEG recordings from a group of 18 patients with focal epilepsy comprising a total of 117 h, we observe a characteristic decrease in synchronization prior to 26 out of 32 analyzed seizures at a very high specificity as tested on interictal recordings. The duration of this preictal state is found to range from several minutes up to a few hours. Investigation of the spatial distribution of preictal desynchronization indicates that the process of seizure generation in focal epilepsy is not necessarily confined to the focus itself but may instead involve more distant, even contralateral areas of the brain. Finally, we demonstrate an intrahemispheric asymmetry in the spatial dynamics of preictal desynchronization that is found in the majority of seizures and appears to be an immanent part of the mechanisms underlying the initiation of seizures in humans.

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1. Introduction

An important issue in epileptology is the question whether epileptic seizures can be anticipated prior to their occurrence. Of particular interest is the question

whether apart from clinical prodromi (which are found only in some of the patients; cf. [Rajna et al., 1997](#)) characteristic and objective features can be extracted from the continuous EEG that are predictive of an impending seizure. Much research has been done on this topic, and recent studies have shown that certain measures derived from the theory of dynamical systems are to some extent capable of extracting information from the EEG that allow the definition of a preictal state.

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After some early work on the predictability of seizures dating back to the 1970s (Viglione and Walsh, 1975), attempts to extract seizure precursors from the EEG were carried out by different groups using mostly linear approaches such as spectral analysis (Rogowski et al., 1981; Duckrow and Spencer, 1992) or pattern detection by analyzing spike occurrence (Gotman et al., 1982; Siegel et al., 1982; Lange et al., 1983; Wieser, 1989; Katz et al., 1991).

First attempts to use nonlinear time series analysis were started in the early 1990s (Iasemidis et al., 1990, 1994) using the so-called largest Lyapunov exponent to describe changes in brain dynamics. The first studies to describe characteristic changes shortly before an impending seizure in a larger group of patients used the so-called correlation dimension as a measure for neuronal complexity in the EEG (Lehnertz and Elger, 1995, 1998; Elger and Lehnertz, 1998) or the correlation density (Martinierie et al., 1998). These studies were followed by others employing measures such as dynamical similarity (Le Van Quyen et al., 1999, 2000, 2001a; Navarro et al., 2002) or dynamical entrainment (Iasemidis et al., 2001). In a recent study, certain signal patterns (“bursts”) and changes in signal energy were reported to be of predictive value (Litt et al., 2001).

A problem with most of the studies presented to date is that the measures used to characterize the EEG are difficult to interpret in terms of their physiological correlate. Also, since almost all of these measures are univariate, i.e. related to only a single recording site, they fail to reflect any interactions between different regions of the brain. The epileptogenic process on the other hand is commonly accepted to be closely associated with changes in neuronal synchronization. The analysis of synchronization in the EEG can, therefore, a priori be regarded as a promising approach for the investigation of the spatiotemporal dynamics of ictogenesis.

In our earlier work, we have analyzed the degree of phase synchronization between EEG signals from different recording sites and found the measure proposed by us to be sensitive to both physiological and pathological synchronization. In particular, we have exemplarily demonstrated the phenomenon of a distinct drop in synchronization prior to three seizures of mesial temporal origin that is usually not observed during the interictal state. This decrease in synchro-

nization was found to occur well in advance, sometimes hours before a seizure, leading us to conclude that a seizure may be seen as the mere “tip of the iceberg” in the sense of it being the climax of successive changes in brain dynamics that start long before the actual seizure (Mormann et al., 2000). These findings have since then been confirmed by another study (Le Van Quyen et al., 2001b) qualitatively describing preictal drops in phase synchronization in neocortical epilepsies.

In this paper, we present, to our knowledge for the first time, a controlled study that examines changes in phase synchronization prior to epileptic seizures. We characterize the degree of synchronization between EEG signals recorded continuously from different locations within the brain and analyze changes over time. Employing an automated technique for the detection of drops in synchronization (Mormann et al., 2003), we investigate whether these drops are indeed characteristic of the preictal period and whether their occurrence can be used as a sensitive and specific criterion for the definition of a pre seizure state and for the distinction of this state from the interictal interval. After confirming our results via cross-validation, we examine the spatial distribution of these preictal drops in synchronization and discuss underlying neuronal mechanisms leading to the initiation of seizures.

2. Materials and methods

2.1. Patient characteristics and data acquisition

The analyzed EEG signals were recorded from 18 epilepsy patients with medically intractable focal epilepsies undergoing invasive presurgical diagnostics between 1993 and 2000 at the Department of Epileptology of the University of Bonn, Germany. Since the localization of the epileptic focus could not be accomplished by means of noninvasive recordings, intracranial electrodes were implanted for the purpose of identifying the focal seizure origin as a prerequisite for possible epilepsy surgery. Apart from the approval by the local medical ethics committee, informed consent for the study was obtained from all patients.

The inclusion criteria for the analyzed data were as follows: data sets for each patient had to include at minimum one seizure with at least 10 min recording

time before seizure onset and at least one interictal recording of at least 15 min length to serve as control. During interictal control recordings, patients had to be awake and at rest. The occurrence of spikes or other interictal epileptiform activity did not serve as an exclusion criterion since spikes can be considered the hallmark of the epileptic brain and any approach for seizure anticipation restricted to nonspike EEG must be regarded as rather limited in application. Only patients with a postsurgical follow-up interval of at least one year were included in order to provide a reliable classification of outcome according to Engel et al. (1993). Patients with outcome 1A and 1B were considered seizure-free after surgery. All recording epochs were free from major artifacts, subclinical seizures, auras, electrical or magnetic stimulation, photostimulation, and hyperventilation unless stated otherwise. Epochs were selected by EEG technicians prior to and independently from the design of this study. Detailed patient characteristics are given in Table 1.

Since opinions differ as to how long before a seizure the mechanisms leading to this event actually begin, any recordings within 4 h prior to seizure onset were

excluded from the set of interictal controls and instead regarded as potentially preictal recordings. In order to neglect the postictal period, which is known to be accompanied by alterations in the EEG, recordings within 1 h after a seizure were discarded from the analysis. Although these alterations usually cease no later than 1 h after seizure onset, there are rare phenomena such as Todd's paralysis that can last up to 48 h after a seizure. Since it would be imaginable that the same long-lasting postictal changes in brain function that act to suppress subsequent seizures, as has been demonstrated in animal models (Sato and Moriwake, 1984), could prevent spontaneous occurrence of "false positive" desynchronizations, we would like to note that for the majority of patients (12 out of 18) no recordings within 48 h after a seizure were used and that only for one patient (patient 18) a larger portion (>50%) of the interictal recordings was taken from this period.

Different interictal data sets were usually recorded on different days. The average length of the 73 analyzed interictal EEG recordings was 40 min. The total amount of data analyzed, including seizure recordings,

Table 1
Patient characteristics

| Patient ID | Gender | Side of onset | Region of onset | Age (years) | Duration of epilepsy (years) | Type of surgery | Histopathology | Seizure-free after surgery | Follow-up (years) |
|------------|--------|---------------|------------------|-------------|------------------------------|----------------------|----------------|----------------------------|-------------------|
| 1 | M | L | Mesial | 38 | 15 | SAH | AHS | Yes | 7 |
| 2 | M | L | Mesial | 22 | 14 | SAH | AHS | Yes | 7 |
| 3 | M | R | Mesial | 34 | 11 | SAH | AHS | Yes | 6 |
| 4 | M | L | Mesial | 39 | 37 | SAH | AHS | Yes | 5 |
| 5 | M | R | Mesial | 10 | 9 | SAH | AHS | Yes | 4 |
| 6 | F | L | Mesial | 28 | 11 | SAH | AHS | Yes | 4 |
| 7 | F | R | Mesial | 31 | 23 | SAH | AHS | Yes | 4 |
| 8 | M | L | Mesial | 28 | 9 | SAH | AHS | Yes | 3 |
| 9 | F | L | Mesial | 29 | 20 | SAH | AHS | Yes | 3 |
| 10 | F | L | Mesial | 37 | 31 | SAH | AHS | Yes | 2 |
| 11 | M | R | Temporal | 29 | 15 | 2/3TLR | GL | Yes | 1 |
| 12 | M | L | Temporal-lateral | 30 | 16 | + SAH + L T + SPT | VE | No | 1 |
| 13 | F | L | Mesial | 46 | 32 | SAH | AHS | No | 3 |
| 14 | F | L | Temporal | 36 | 15 | SAH + PR | GL | No | 1 |
| 15 | F | L | Mesial | 34 | 16 | SAH | AHS | No | 5 |
| 16 | F | L | Occipital | 30 | 19 | EL + SPT | CM | No | 3 |
| 17 | F | L | Mesial | 25 | 18 | SAH | w.p.f. | No | 2 |
| 18 | F | R | Temporal | 60 | 30 | 2/3TLR + SAH | GL | Yes | 2 |

Types of surgery: SAH, Selective Amygdalo-Hippocampectomy; 2/3TLE, 2/3 Temporal Lobe Resection; L, Lesionectomy; T, Topectomy; SPT, Subpial Transections; PR, Pole Resection; EL, Extended Lesionectomy. Histopathological findings: AHS, Ammon's Horn Sclerosis; VE, Virus Encephalitis; GL, Gliosis; CM, Cortical Malformation; w.p.f., without pathological findings.

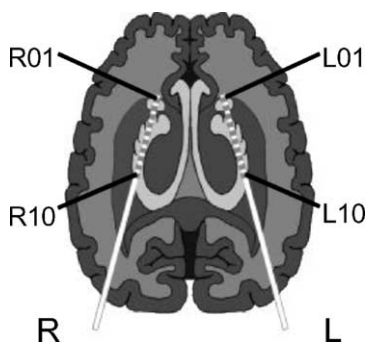


Fig. 1. Schematic view of intrahippocampal depth electrodes.

was more than 117 h. Detailed summary of recording times is given in Table 2.

EEG recordings were performed under video control using chronically implanted silastic intrahippocampal depth electrodes (see Fig. 1 for a schematic view of implantation) and subdural strip or grid electrodes. For the present study we restricted ourselves to the analysis of EEG recorded via intrahippocampal depth electrodes, each equipped with 10 cylindrical contacts of a nickel–chromium alloy (length: 2.5 mm, intercontact distance: 4 mm). These electrodes were implanted stereotactically via the longitudinal axis of the hippocampus using an occipital approach with the amygdala as target for the most anterior electrode contact (cf. Van Roost et al., 1998). After neurosurgical implantation, the correct placement of the electrodes was verified by magnetic resonance imaging.

EEG recordings were carried out on a 128-channel amplifier system with band-pass filter settings of 0.5–85 Hz (12 dB/oct.) using a common average reference. The sampling rate was 173.61 Hz, and analog–digital conversion was performed at 12-bit resolution.

2.2. Measuring phase synchronization

Phase synchronization (Huygens, 1673) is traditionally defined as the locking of the phases of two oscillating systems. In order to obtain the phases of our continuous EEG signals, we followed the *analytic signal* approach (Gabor, 1946) which renders an unambiguous definition of the so-called *instantaneous phase* for an arbitrary signal based on the *Hilbert Transform* of that signal (Panter, 1965).

Following the work of Rosenblum et al. (1996) and Tass et al. (1998) in understanding phase syn-

chronization in a statistical sense, we used the *mean phase coherence* R (Mormann et al., 2000) to measure the degree of phase synchronization between two EEG segments. By definition R ranges from 0 to 1 where high values indicate a high degree of phase synchronization and low values are obtained for unsynchronized signals. We would like to mention that in some recent publications, the mean phase coherence has been used under the name of “first Fourier mode” and “phase locking value”.

2.3. Data analysis

The recorded data were analyzed using a moving-window technique (Barlow, 1985). EEG signals were divided into segments of 4096 sampling points each, corresponding to a window length of 23.6 s at the given sampling rate. Windows overlapped by 20% so the distance in time between two consecutive windows was 18.9 s. This window length can be regarded as a compromise between the required statistical accuracy for the calculation of the mean phase coherence and approximate stationarity within a window’s length (Lopes da Silva, 1987; Blanco et al., 1995).

Prior to the calculation of the mean phase coherence, three steps of data preprocessing were carried out for each window: first, the data in each window were demeaned. Next, to avoid edge effects, each window was tapered using a cosine half wave before performing the Hilbert Transform. Finally, since the calculation of the Hilbert Transform in principle requires integration over infinite time, which cannot be performed for a window of finite length, 10% of the calculated instantaneous phase values were discarded on each end of every window.

For each EEG recording, the mean phase coherence R was computed for every possible combination of different recording contacts i and j (10 in each hemisphere) for every consecutive window resulting in 190 different time profiles $R_{ij}(t)$ for every recording.

2.4. Detecting preictal desynchronization

Our aim in this study was to investigate whether the period preceding a seizure is characterized by a global or local decrease in synchronization and whether this decrease can serve as a criterion to distinguish this period from the interictal interval.

Table 2
Seizure anticipation based on preictal desynchronization

| Patient ID | Interictal recordings | Interictal recording time (min) | Seizure ID | Preictal recording time (min) | Channel combinations with preictal desynchronization | Anticipation time (min) |
|------------|-----------------------|---------------------------------|------------|-------------------------------|---|-------------------------|
| 1 | 3 | 64 | 1a | 24 | L5/6; R2/3 | >21 |
| | | | 1b | 78 | L5/6; L6/7; L7/8; L9/10; R2/3 | 56 |
| 2 | 5 | 162 | 2a | 57 | L1/2 ; R5/6; R9/10 | >219 |
| | | | 2b | 100 | L1/2 | >127 |
| 3 | 2 | 39 | 3a | 31 | L7/8; R5/6 | 8 |
| | | | 3b | 10 | L7/8 | 4 |
| 4 | 6 | 129 | 4a | 24 | L1/2 ; L3/4 | 120 |
| 5 | 1 | 15 | 5a | 20 | L1/2; L2/3; L3/4 ; L7/8 ; L8/9; R6/7; R7/8 | >18 |
| 6 | 2 | 36 | 6a | 105 | L3/4; L4/5 ; L5/6; R4/5 | >141 |
| 7 | 1 | 20 | 7a | 33 | R8/9 | 104 |
| | | | 7b | 21 | L1/2; L3/4; R1/2; R7/8; R9/10 | 201 |
| 8 | 7 | 140 | 8a | 33 | R6/7 | 13 |
| 9 | 2 | 91 | 9a | 39 | – | – |
| 10 | 6 | 192 | 10a | 97 | – | – |
| 11 | 3 | 78 | 11a | 171 | L5/6; L6/7 | 46 |
| 12 | 1 | 28 | 12a | 133 | L4/5 ; L6/7; L7/8; L8/9; L9/10; R1/2; R4/5; R7/8 | 143 |
| | | | 12b | 65 | L1/2; L6/7; L8/9; L9/10; R1/2; R4/5; R5/6; R6/7; R7/8 ; R8/9 | 117 |
| | | | 12c | 17 | L1/2 ; L4/5; L6/7; L7/8; L8/9; R1/2; R3/4; R4/5; R5/6; R7/8 | >15 |
| | | | 12d | 10 | L1/2; L8/9; R1/2; R3/4; R4/5 ; R5/6; R6/7; R7/8 | >8 |
| 13 | 9 | 293 | 13a | 55 | – | – |
| 14 | 4 | 253 | 14a | 217 | L8/9 ; R2/3; R7/8 | 151 |
| 15 | 2 | 34 | 15a | 25 | R1/2 ; R2/3; R9/10 | >22 |
| | | | 15b | 19 | L3/4; L5/6; R1/2 | >63 |
| 16 | 4 | 85 | 16a | 111 | L9/10 | 85 |
| | | | 16b | 22 | L5/6 ; L6/7; R4/5; R5/6; R6/7 | >19 |
| 17 | 6 | 614 | 17a | 76 | – | – |
| | | | 17b | 61 | – | – |
| 18 | 11 | 657 | 18a | 240 | L7/8; R1/2 | 200 |
| | | | 18b | 240 | R1/2 | 176 |
| | | | 18c | 236 | R4/5 | 221 |
| | | | 18d | 240 | L7/8 | 142 |
| | | | 18e | 240 | – | – |

Channel combinations exhibiting the longest decrease in synchronization per seizure are marked in bold. Anticipation times exceeding preictal recording times are due to gaps in these recordings. Seizures 2a and 10a were preceded by hyperventilation.

In order to obtain a baseline for the interictal state, we calculated mean value m_{ij} and standard deviation σ_{ij} by averaging the values of the time profiles $R_{ij}(t)$ over all interictal recordings from the respective patient for every combination of channels i and j .

In relation to any given baseline, a local drop can be characterized by two independent parameters: its depth and duration. The depth of such a drop may be measured in units of the standard deviation of the baseline epoch, whereas its duration can be quantified by the number of minutes during which the mean value of a profile drops below a certain threshold.

For a practical implementation, we used a backward moving average filter of width d to smoothen the time profiles of $R_{ij}(t)$ and defined a detection of preictal desynchronization if the smoothened profiles $R_{ij}^d(t)$ dropped below the interictal mean m_{ij} by more than r standard deviations σ_{ij} . Note that this technique is equivalent to using a moving window technique, measuring the area between the interictal reference level and the course of the original (unsmoothed) profile within a window of length d , and comparing this area to a rectangular reference area of width d and a height of r interictal standard deviations. Thus, we obtained two parameters r and d that govern the mean depth of a drop over a certain time to be used as a threshold for the detection of preictal desynchronization (Mormann et al., 2003).

In order to estimate both sensitivity and specificity of our method, we applied it to all preictal and all interictal recordings, respectively. Taking into account that the statistical significance of the synchronization profiles increases with the mean level of synchronization which in turn decreases with increasing distance between EEG contacts (cf. Mormann et al., 2000), we restricted the following analysis to neighboring channel combinations, thus reducing the number of profiles to 18.

2.5. Parameter optimization

In order to determine suitable values for the two parameters r and d , we carried out an in-sample optimization for the entire group of patients by maximizing the performance P of our method defined as:

$$P = \sqrt{\frac{(\text{Se}^2 + \text{Sp}^2)}{2}}$$

where Se is the sensitivity, defined as the percentage of seizures for which a preictal desynchronization could be detected and Sp the specificity rate, defined as 1 minus the average number of false positive detections per hour of interictal EEG (for more than 1 false positive per hour, Sp was set to zero for that particular combination of r and d). For the optimization, the parameter r was varied from 0 to 6 standard deviations in steps of 0.2, and d was varied from 1 to 30 analysis windows (corresponding to 0–6 min). For the calculation of the specificity rate, the duration of each interictal recording was reduced by the length d of the backward moving average window keeping it thereby proportional to the specificity (ratio of true negatives to number of points in the smoothened profile). Note that there are other ways of defining a performance, e.g. by normalizing the specificity to the duration of the preictal recordings available for each respective patient, and that all of these represent a certain weighting of sensitivity and specificity. For our purpose, we have deliberately chosen a performance measure that puts a high emphasis on specificity.

It is important to point out that no a posteriori knowledge in the sense of a “best channel selection” was used, which would have required an appropriate statistical correction for multiple testing. For a true positive *at least one* of the channel combinations analyzed needed to exhibit a decrease in synchronization while for a true negative *all* combinations needed to be free of drops in synchronization.

2.6. Cross-validation

When performing an in-sample parameter optimization, there is a risk of overtraining an algorithm in the sense that parameters are optimized on a given sample to yield a performance for this sample (estimated performance) that may not be achieved in an out-of-sample trial (true performance). To reduce the risk of an over-estimation of our method’s performance due to in-sample optimization, we performed a cross-validation analysis.

For the given sample of patients, an 18-fold cross-validation was carried out using the “leaving-one-out” method (cf. Vapnik, 1982; Cherkassky and Mulier, 1998), i.e. each of the 18 patients was subsequently used as a test sample while the remaining 17 patients served as training samples, i.e. for parameter optimiza-

tion. The overall performance of the respective test samples was then compared to the performance of the entire group as defined in the previous section. Similar values for both performance estimates indicate that parameters were not overtrained. The standard error of the sensitivity is given by:

$$E_{Se} = \sqrt{\frac{Se(1 - Se)}{n}}$$

where n is the number of test cases (i.e. $n = 18$ in this study). The standard error for the specificity E_{Sp} is calculated accordingly, and the resulting error of the

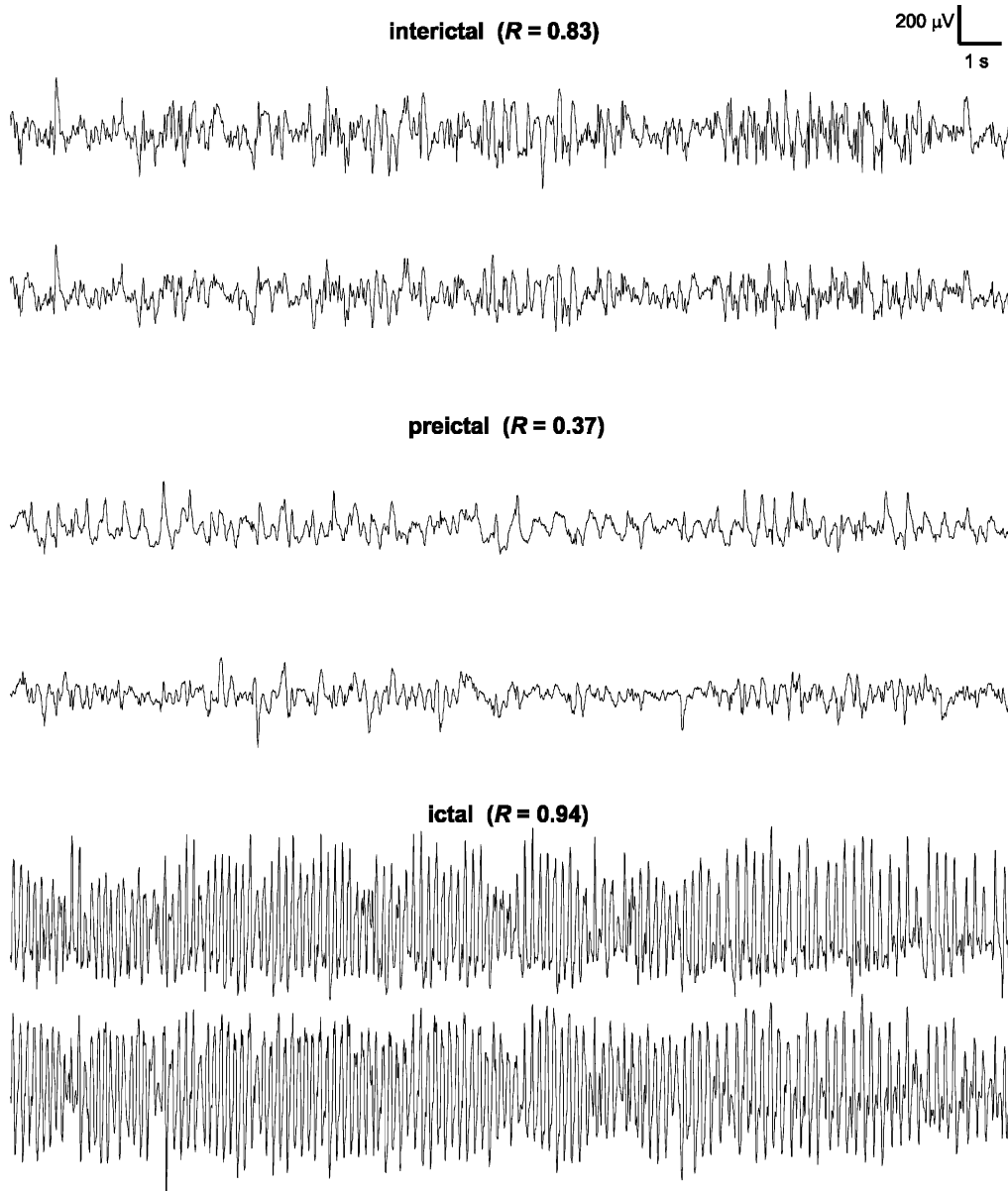


Fig. 2. Exemplary EEG segments of one patient from the interictal, preictal, and ictal period and respective values of the mean phase coherence R calculated from these segments.

performance E_P can be obtained using Gaussian error propagation.

3. Results

Fig. 2 shows a sample of typical EEG segments of a patient from the interictal, preictal, and ictal period. For each period, EEG segments from two neighboring channels are displayed along with the degree of synchronization between them as measured by the mean phase coherence R .

In Fig. 3, two typical examples of a preictal decrease in synchronization are presented. Displayed are the synchronization profiles between two neighboring recording sites for two patients (patients 7 and 14 in Table 1) for both an interictal and a periictal EEG recording.

Such a decrease in synchronization prior to seizure onset could be found in almost all of the periictal

recordings, although usually only in a few of the 18 possible combinations of neighboring channels.

In order to quantify this observation, the optimization process was carried out for the entire sample of recordings as described in the Section 2. Optimum performance could be obtained for values $r = 4$ and $d = 8$ windows (corresponding to 2.5 min) and amounted to $P = 91\%$ for the entire group.

Using these parameters, a preictal decrease in synchronization was found before 26 out of 32 seizures. In terms of patients, drops in synchronization prior to all seizures were found in 13 of the 18 patients analyzed in this study. Restricting our view to the homogeneous subgroup of the 10 patients with unilateral mesial temporal lobe epilepsy as confirmed by complete postoperative seizure control (outcome Engel class 1) after selective amygdalo-hippocampectomy, we found preictal desynchronization in 12 out of 14 seizure recordings corresponding to 8 out of 10 patients. For the entire group of patients, there was not

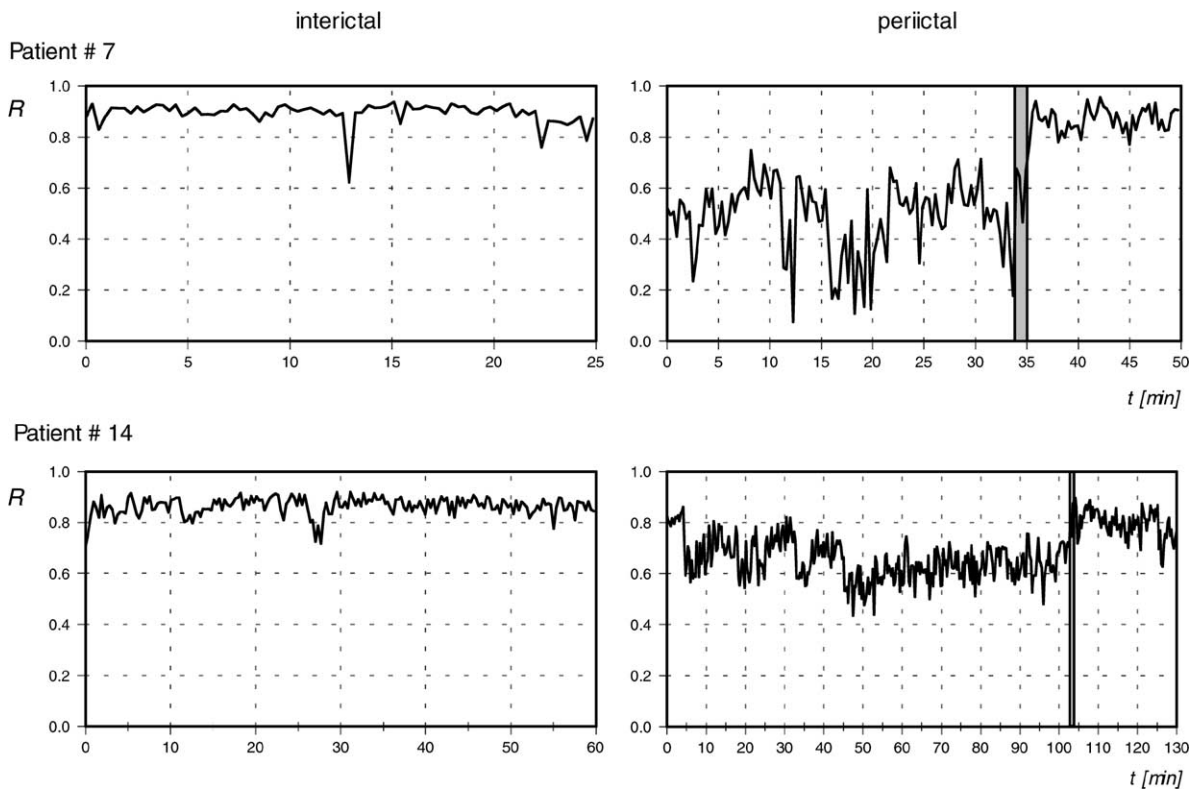


Fig. 3. Interictal and periictal synchronization profiles from two patients (patients 7 and 14). Seizures are marked by gray vertical bars.

a single false positive detection during the entire 48 h of interictal recordings, corresponding to a specificity of 100%. The results for each patient are displayed in detail in Table 2.

The duration of the detected preictal state could not exactly be determined in most cases since the preictal state had already started at the beginning of the periictal recordings (cf. Fig. 3). Anticipation horizons were defined as the time interval between the first positive detection of preictal desynchronization found in any of the combination of neighboring channels during the potentially preictal period of 4 h before seizure and the seizure onset and ranged, as determined from the data available, from 4 min up to 221 min.

For patients with more than one seizure with preictal desynchronization, we found that although the desynchronization was usually restricted to a few channel combinations, in most cases there was at least one combination for which a preictal desynchronization was found for all seizures of a particular patient. Also, it was usually this combination that exhibited the most prominent drops in synchronization (cf. Table 2).

During the actual seizure activity, the usual finding was a steep increase in synchronization reaching or even surpassing the interictal mean value. Analyses of the preictal drops revealed that in 17 out of the 26 detected preictal states, at least for one combination the preictal drop lasted until the onset of the seizure whereas in the remaining cases, the preictal synchronization level rose above the detection threshold before (although usually very close to) seizure onset.

In order to check for overtraining due to in-sample optimization, an 18-fold cross-validation was performed as described in the Section 2. Results yielded a corrected performance of $P = 85\%$ that did not deviate from the in-sample performance of $P = 91\%$ by more than the standard error of $E_P = 8\%$.

As for the spatial distribution of the described effects, Fig. 4 shows an example of the spatial characteristics of the preictal drop in phase synchronization as measured by the mean phase coherence (seizure 15b, cf. Table 2). For the spatial analysis, all 190 channel combinations were subjected to the algorithm for detecting preictal desynchronization. The combinations with positive detections are marked by gray

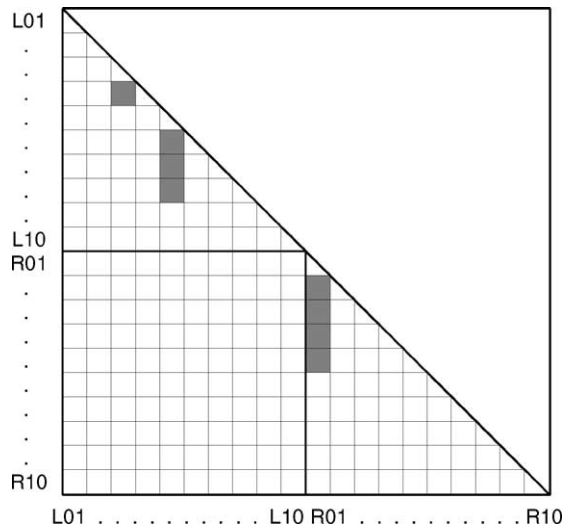


Fig. 4. Spatial distribution of the preictal decrease in synchronization for one exemplary seizure (seizure 15b, cf. Table 2). Channel combinations for which a preictal desynchronization was detected are marked by gray squares.

squares. Note that out of the three combinations of neighboring channels for which a drop in synchronization is found, in two cases the desynchronization appears to have a clear direction as illustrated by the vertical “string” of positive combinations: in the right hemisphere, there is a desynchronization of contact 1 with the successive contacts 2 through 5. In the left hemisphere, contact 5 is desynchronized with the successive recording sites (contacts 6 through 8) but remains synchronized with all preceding recording sites (contacts 1 through 4). Such an intrahemispherical asymmetry in the sense of an either horizontal or vertical string of drops in synchronization was found in 16 out of the 26 patients with preictal decrease in synchronization.

4. Discussion

Results show that in more than 80% of the analyzed seizures, the period preceding the seizure is characterized by a decrease in synchronization between certain recording sites. This decrease in synchronization can be detected by the automated technique used in this study and was not found during the interictal interval.

The optimization of the parameters used in the detection algorithm was carried out for the entire group of patients and can be considered for the most part free from overtraining as confirmed by cross-validation. The obtained specificity of 100% is not surprising as it is due to the strong emphasis on specificity used in the parameter optimization process. A weaker emphasis on specificity might have yielded an even better sensitivity for our group of patients but at the expense of a decreased specificity. In this context, it is important to keep in mind that for a test involving one or more threshold parameters, the choice of these parameters always represents a tradeoff between the sensitivity and specificity of this test and that one of these quantities can always be increased at the expense of the other. A study neglecting the specificity of an observed phenomenon must, therefore, be regarded as very limited in significance. Nevertheless, most of the studies presented to date (e.g. [Martinerie et al., 1998](#); [Le Van Quyen et al., 1999, 2000, 2001a,b](#); [Jeger et al., 2001](#)) have not systematically investigated the specificity of the employed methods.

4.1. Why a decrease in synchronization?

Most theories on seizure generation are based on the concept of a “critical mass” of neurons that are progressively involved in synchronized high-frequency discharging and eventually induce actual seizure activity ([Yaari and Beck, 2002](#)). Since an epileptic seizure is traditionally assumed to be associated with an *increase* in neuronal synchronization, it is at first surprising to observe a *decrease* in synchronization prior to seizures. In our earlier work, we have offered two hypotheses to explain this phenomenon ([Mormann et al., 2000](#)): the first hypothesis is that all affected recording sites are located within a region of the brain that is in an “idle” state of low synchronization. The neurons within this region might then easily be recruited into a critical mass of pathologically synchronized neuronal tissue, corresponding to an increased susceptibility for a rapidly expanding process of pathological synchronization. The second hypothesis is that the drop in synchronization is observed between two recording sites belonging to two different regions where one corresponds to neuronal tissue already involved in the pathological synchronization progressing from the epileptic focus

while the other is not yet affected by the focus and still takes part in some physiologically synchronized process.

The spatial distribution of the preictal loss of synchrony provides evidence that the second hypothesis is to be favored: if a macroscopic region of the brain were in an “idle” state, one would expect to find a drop in synchronization in most of the neighboring channel combinations, which for the majority of patients is not the case. Instead, in the example given in [Fig. 4](#), there are only three disjoint combinations of neighboring channels in the given example that show a drop in synchronization. The intrahemispherical asymmetry described in the [Section 3](#) could be interpreted in the sense that instead of a bilateral desynchronization between two macroscopic regions of the brain, the small region surrounding contact 5 appears to become “torn out” of its physiological state of synchronization with the successive recording sites and is possibly forced into synchronization with some slowly expanding region of pathologically synchronized neuronal tissue emanating from the direction of the preceding contacts.

From these considerations, it follows that the preictal decrease in synchronization observed in this study could be regarded not merely as a necessary condition for the sudden emergence of a seizure but instead as an immanent part of the mechanisms of ictogenesis taking place long before the actual onset of a seizure.

It appears, therefore, that long-term spatial shifts in synchronization play an important role in the facilitation of seizures. Whether the observed effects reflect the expansion of areas synchronized by the focus or rather the break down of inhibitory mechanisms protecting other brain areas from being affected by the focus, remains subject for further investigation. We expect the spatiotemporal analysis of preictal desynchronization to be of great value in this field of research.

4.2. Location of preictal desynchronization

Concerning the location of the observed preictal drops in synchronization, it turned out that for half of the unilateral mesial temporal subgroup of patients with preictal drops in synchronization (4 out of 8), the most prominent drops were found in the hemisphere contralateral to the focal area while for the

remaining patients they were found on the ipsilateral side although not necessarily within the focal area (as determined by electrographical seizure onset). This finding stands in agreement with earlier studies (e.g. Le Van Quyen et al., 2000; Iasemidis et al., 2001) while in other studies seizure precursors were mostly found within or near the focal area (e.g. Lehnertz and Elger, 1998; Litt et al., 2001). The spatial distribution of preictal desynchronization indicates that the process of seizure generation in focal epilepsy is not necessarily confined to the focal area but may instead involve more distant, even contralateral areas of brain tissue. This interpretation is supported by other studies presenting evidence for an involvement of the contralateral hippocampus in the epileptogenic process in patients with temporal lobe epilepsy (Ende et al., 1997; Briellmann et al., 1998; Grunwald et al., 1999; Staba et al., 2002) and animal models (Yasuda et al., 2001).

4.3. Anticipation times

The duration of the anticipation times as given in Table 2 is mostly of the order of 1 h or more rather than just a few minutes which stands in contrast to earlier studies (Elger and Lehnertz, 1998; Lehnertz and Elger, 1998; Martinerie et al., 1998; Le Van Quyen et al., 1999, 2000, 2001a; Navarro et al., 2002) where mean anticipation times from 2 to 11 min were described. The different range of anticipation times implies that changes in dynamics tracked by synchronization measures are different from those tracked by other nonlinear measures. It should not be omitted that in two recent studies (Iasemidis et al., 2001; Litt et al., 2001) similar anticipation times have been reported as found in this study. Whether these findings reflect the same dynamical aspects, remains to be investigated. It should be pointed out that with the given anticipation horizons in the range of hours, there is little information about when exactly the seizure will occur. We, therefore, avoid the term “prediction” and rather speak of “anticipation” of seizures implying that we may know that a seizure has a certain probability to occur within a certain time frame but we do not know exactly when. Nevertheless, anticipation horizons as extended as found in this study would definitely leave enough time for possible strategies to prevent the occurrence of a seizure.

4.4. Future perspectives

In contrast to earlier studies (Le Van Quyen et al., 1999; Iasemidis et al., 2001) where electrode sites exhibiting predictive features were reported to change from seizure to seizure for the same patient, we found the channel combinations with prominent drops in synchronization to be constant over seizures for most patients. This constancy could be used to further improve the specificity of the method by only considering channel combinations for a respective patient that have proven to be sensitive for characterizing the preictal state and thus omitting possible false positive detections in the remaining channel combinations. Another way to improve the method's performance in long-term evaluations could be an individual parameter adjustment for each patient to obtain the best possible discrimination between interictal and preictal states. It should be pointed out, however, that both of these improvements would require a posteriori knowledge that would need to be obtained by extensive preanalysis. In this context, it is important to once again emphasize that the results reported in this paper were obtained from a retrospective study on selected data samples in the sense that, for instance, any sleep recordings were excluded from the analysis. The sensitivity and specificity obtained in this study might, therefore, significantly differ from what one would find in a prospective study. The aim of this study was merely to examine whether the finding of a preictal decrease in synchronization could be confirmed in a larger group of patients and whether this phenomenon can be used as a criterion to distinguish the pre-seizure period from the interictal interval. From our preliminary experience with long-term recordings, we would conjecture that including additional interictal data covering different states of vigilance (especially sleep) could diminish the predictive performance whereas best channel selection and patient-specific parameters are on the other hand likely to result in an increase in performance.

Once given a sufficient sensitivity and specificity for prospective seizure anticipation, a variety of new therapeutic strategies could be envisaged. In a first step, one might consider control of established presurgical evaluation techniques in a clinical setting, e.g. timely injection of a suitable SPECT tracer, or an improved control of recent seizure prevention techniques like

vagal nerve stimulators (Scherrmann et al., 2001) but also the development and exploration of new prevention techniques in humans. Among others, these include on-demand and local application of short-acting, powerful drugs (cf. Eder et al., 1997; Stein et al., 2000), electrical intervention techniques (Schiff et al., 1994; Velasco et al., 2000; Gluckman et al., 2001), local cooling (Hill et al., 2000), or biofeedback operant conditioning (cf. Sterman, 2000) by applying neuropsychological or behavioral tools such as sensory processing, motor tasks, or memory processing.

5. Conclusion

The analysis of synchronization between EEG signals recorded simultaneously from different locations in the brain has shown that a large majority of analyzed seizures are preceded by a decrease in synchronization between certain recording sites. By investigating the suitability of this phenomenon for a characterization of the preictal state, we have shown that it is in principle possible to discriminate the preictal from the interictal state, which makes the method used in this study a promising concept for prospective seizure anticipation. In addition, we have provided evidence that the process of seizure generation in focal epilepsy is not necessarily confined to the focal area and have demonstrated that the preictal changes in synchronization, which start long before the actual onset of a seizure, appear to be an immanent part of the mechanisms underlying seizure generation in humans.

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