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Early Seizure Detection

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Summary: For patients with medically intractable epilepsy, there have been few effective alternatives to resective surgery, a destructive, irreversible treatment. A strategy receiving increased attention is using interictal spike patterns and continuous EEG measurements from epileptic patients to predict and ultimately control seizure activity via chemical or electrical control systems. This work compares results of seven linear and nonlinear methods (analysis of power spectra, cross-correlation, principal components, phase, wavelets, correlation integral, and mutual prediction) in detecting the earliest dynamical changes preceding 12 intracranially-recorded seizures from 4 patients. A method of counting standard deviations was used to compare across methods, and the earliest departures from thresholds determined from non-seizure EEG were compared to a neurologist's judgement. For these data, the nonlinear methods offered no predictive advantage over the linear methods. All the methods described here were successful in detecting changes leading to a seizure between one and two minutes before the first changes noted by the neurologist, although analysis of phase correlation proved the most robust. The success of phase analysis may be due in part to its complete insensitivity to amplitude, which may provide a significant source of error. **Key Words:** Prediction—Epilepsy—Nonlinear—Power spectrum—Correlation—Dimension.

Whether epileptic seizures can be predicted by quantitative analysis methods applied to EEG has been a focus of much recent interest (Lehnertz and Elger, 1998; Le Van Quyen et al., 1999; Schiff, 1998). This resurgence of interest has been motivated by several factors, including the proliferation of powerful new methods for analyzing nonlinear system dynamics, as well as interest in developing epilepsy control devices. Nevertheless, attempts to detect seizures automatically from EEG are not new, and older linear analysis methods showed promise nearly 20 years ago (Lange et al., 1983; Rogowski et al., 1981).

Rather than referring to a declaration in advance of the time and location of a seizure, the term *prediction* has frequently been used to refer to the process of identifying a state from the EEG that precedes a clinical seizure that is known to have occurred. Using this meaning, the period of prediction refers to the time between identification of a preseizure state and either the onset of the clinical seizure or the time at which a well-trained clinician can pick up evidence of changes by visual inspection of the EEG. From the point of view of designing a control device, the distinction between clinical and neurologist-determined onset may be meaningless—the device simply needs to detect the seizure dynamics early enough to permit effective intervention. From a clinical perspective, what is meaningful is whether the fact that a seizure is about to occur can be determined reliably when the future is unknown. Successful completion of this goal,

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which entails "prediction" in a slightly but crucially different sense from that just described, can only be shown by validating the method on out-of-sample data, in which the location or even the presence of seizures is unknown to the tester, and false-positive/false-negative detection rates can be established to determine sensitivity and specificity.

To facilitate meaningful comparisons between EEG analysis techniques reported commonly in the seizure prediction literature, we performed a set of analyses on a common dataset of 12 intracranially recorded seizures from four children undergoing presurgical evaluation for intractable epilepsy, chosen to represent a range of spatial extent, location, and type of underlying pathology. A battery of both linear and nonlinear methods (power spectral density, cross-correlation, principal component analysis, phase synchronization, wavelet packet analysis, correlation dimension, and mutual nonlinear prediction) was applied to the same set of 12 seizures to characterize the earliest dynamic changes leading up to the clear onset of an epileptic seizure.

Clinical EEG interpretation and time series analysis of seizure EEG have traditionally been conducted separately, by specialists with very different training and without awareness of each other's techniques and conclusions. This division has contributed to a fragmented knowledge base and has limited the practical application of results to relieving patient suffering. Seeking to avoid such fragmentation, close consultation with a clinician was maintained throughout these investigations, and the final results were compared with judgments made by a neurologist who is board certified in electroencephalography (S.W.)—still the "gold standard" in seizure identification.

Inspection of the raw ictal EEG suggests that an increase in coherent neuronal behavior occurs during seizures. Each of the seven methods presented has been applied previously with variable success to characterizing this coherent behavior, although the theoretical bases of their approaches differ dramatically. In our opinion, the extreme complexities involved in developing an understanding of seizure dynamics warrant addressing this problem from a variety of viewpoints.

POWER SPECTRUM

Power spectral analysis has been applied to EEG more frequently than any of the other techniques applied here, and it provides the basis for all analyses in the frequency domain. Almost two decades ago, spectral analysis was used to distinguish between epochs not associated with seizures and those preceding the spike–wave bursts of absence seizures with as high as 80% accuracy (Siegel et al., 1982). Siegel et al. (1982) pointed out, however, that each subject's preburst EEG seemed to be characterized by a unique pattern of changes, and that no common prodromal pattern was found that could be applied uniformly across patients. However, when a nonstationary power spectral analysis was applied that computed the instantaneous power spectrum every 0.1 second for 10 seconds preceding a spike and wave complex, the results reflected a relative increase in arrhythmic slow activity leading up to spike and wave complexes in all 10 subjects (Inouye et al., 1994). Increased spectral power at *high* frequencies (40 to 150 Hz) has been noted at the start of seizures beginning with a well-defined pattern of low-amplitude signal, referred to as the *electrodecremental event* (Fisher et al., 1992).

The mechanisms of the electrodecremental EEG pattern remain obscure, despite having been recognized for decades (Jasper, 1964). One central question is whether this period reflects an overall decrease in activity. Fisher et al. (1992) suggested that the electrodecremental period does not indicate a lack of signal, but rather a shift of the spectral energy from lower to higher frequencies. In a study correlating characteristics extracted from the power spectrum of patients with partial epilepsy to surgical outcome (Alarcon et al., 1995), one of the most common early ictal manifestations noted was the generalized electrodecremental event, present in 12 of 15 patients. That study suggested, based on surgical outcome, that these events may not be part of the ictal process itself. Instead, they may reflect generalized cerebral changes that enhance the likelihood of seizure formation in susceptible tissue—consistent with the "two-hit" hypothesis of seizure initiation and propagation.

Application of spectral methods to interictal EEG has revealed increased power in lower frequencies (0.25 to 8 Hz) relative to higher frequencies (8.25 to 30 Hz) when EEGs from epileptic subjects were compared with EEGs from normal subjects and headache patients with normal EEGs (Drake et al., 1998). Spectral analysis of bilateral interictal recordings taken over several days from the mesiobasotemporal lobes showed a striking asymmetry in the variability of the power spectrum that persisted for hours, with what Wang and Wieser (1994) termed the relatively "rigid" side showing 80% coincidence with lateralization of the seizure based on positron emission tomography (Wang and Wieser, 1994).

CROSS-CORRELATION

To our knowledge, autocorrelation was first applied to EEG by Norbert Weiner and his colleagues in 1968

(Wiener, 1969). More recently, autocorrelation was used to assess the likelihood of future neuronal bursts (Colder et al., 1996). Colder et al. (1996) reported decreased likelihood of bursting near the site of seizure onset from sites located within the hippocampus or entorhinal cortex. Shortly after the seizure predictions of Rogowski et al. (1981) of several seconds based on an autoregressive model, cross-correlations between interictal spikes from homologous brain structures were used to demonstrate changes in the EEG up to tens of minutes before the clinical onset of some epileptic seizures (Lange et al., 1983). During the past 20 years, the cross-correlation technique has been applied to EEG in countless studies as one of the more conventional analysis tools against which newer tools are compared. A few of these applications include using cross-correlation for determining the location of epileptogenic foci (Mars and Lopes da Silva, 1983), investigating interdependence of EEG signals (Lopes da Silva et al., 1989), estimating time delays between channels (Harris et al., 1994), and characterizing dynamic properties of sleep EEG (Mann et al., 1993).

PRINCIPAL COMPONENTS ANALYSIS (PCA)

PCA is a linear method that has been used in EEG research to combine information across channels and to reduce the dimensionality of the original multichannel EEG to a smaller set of theoretically meaningful component variables. Accomplishing this involves constructing a linear composite of the original variables by selecting a set of weights that maximizes the variance of the original data. In this case, the number of variables equals the number of electrodes or amplifier channels. To explain 100% of the variance expressed by the original data, the number of principal components extracted from the correlation matrix would be equal to the number of channels, and no reduction in dimensionality would occur. Thus, one must choose an acceptable percentage of the overall variance that one seeks to preserve by calculating its principal components. In 1987, when Maier et al. (1987) used PCA for source localization of human visual evoked potentials, they chose a level of 95%, assuming a noise level of 5% "after prolonged averaging." In the same year, Freeman and van Dijk (1987) reported that using only the first principal component was sufficient for their comparison between spatial patterns in the visual cortex and the olfactory bulb of a rhesus monkey. Nine years later, Barrie et al. (1996) compared results obtained from applying PCA, a modified fast Fourier transform method, and calculation of root mean square amplitudes to extraction of the broad-spectrum waveform common to all channels of an 8×8 electrode array placed on the cortical surface of a rabbit, and found the three methods to yield equivalent spatial patterns. In that same study, they reported the first principal component to account for 90 to 99% of their data variance (Barrie et al., 1996). Jobert et al. (1994) found that after performing PCA on the results of their spectral analysis, the first two principal components retained 89.0 to 99.4% of the initial variance for their 16 subjects, a sufficient amount for their automatic analysis of sleep EEG. A sophisticated algorithm for choosing the number of principal components to extract can be found in the paper by Arruda et al. (1996).

WAVELETS

Originating from the field of seismology (Goupillaud et al., 1984), during the last 15 years wavelet transforms have been applied to a number of problems including data compression (Coifman, 1986; DeVore et al., 1992), turbulence (Argoul et al., 1989), and speech processing (Kadambe and Boudreaux–Bartels, 1992). After the original work by Gotman (1982) using decomposition of the EEG into half waves for automatic seizure detection, there followed a number of applications of wavelet transforms to EEG analysis and seizure detection (Eberhart et al., 1989; Gabor and Seyal, 1992; Gabor et al., 1996; Jando et al., 1993; Ozdamar et al., 1991; Schiff et al., 1994a, b; Webber et al., 1994). Seizure prediction by a mean of 15.5 seconds in 92% of 125 seizures has been reported (Osorio et al., 1998), using a method based on Danbechies' PAUB4 wavelet (Danbechies, 1992).

PHASE CORRELATION

Methods of measuring phase synchrony include those based on spectral coherence (Bressler et al., 1993; Menon et al., 1996), which incorporates both amplitude and phase information, detection of maximal values after filtering (Yordanova et al., 1997), and wavelet filtering (Rodriguez et al., 1999). In their 1996 investigation of phase synchronization of chaotic oscillators, Rosenblum et al. (1996) pointed out that "the notion of synchronization itself lacks a unique interpretation," but settled on the general description of synchronization by Blekhman (1988) as "an appearance of some relations between functionals of two processes due to interaction." They then showed that for weakly coupled nonlinear equations, a condition exists in which the phases are locked, but the amplitudes vary chaotically and are practically uncorrelated. Tass et al. (1998) developed a technique based on this work, which they applied to noisy nonstationary bivariate data from magnetoencephalograms and muscle activity in Parkinson's disease. Stratonovich (1963) described synchronization of noisy systems as the "appearance of peaks in the *distribution of the cyclic relative phase*" that point to preferred phase difference values. To characterize the strength of synchronization, Tass et al. (1998) proposed two indices, one based on Shannon entropy and one based on conditional probability that builds on the idea of Stratonovich (1963), aiming to quantify the degree of deviation of the relative phase distribution from a uniform phase distribution.

CORRELATION DIMENSION

With the advent of nonlinear time series analysis tools that could be applied to experimental data, particularly the correlation integral (Grassberger, 1983), much interest arose in investigating nonlinear dynamics of EEG activity. There has been much discussion aimed at establishing the appropriate and optimal application of these methods. It has been suggested that estimating fractal dimension, a characteristic associated with chaotic systems, may provide additional insight to define a preseizure state or the seizures themselves (Babloyantz and Destexhe, 1986). It has also been pointed out that obtaining evidence of chaotic activity may not be trivial. Osborne and Provencale (1989) showed by obtaining a finite correlation dimension for colored noise that the sole observation of a finite fractal dimension from the analysis of a time series is not sufficient to infer the presence of chaos in the system dynamics. Along the same lines, Theiler's (1995) analysis of an EEG time series reported previously to be chaotic emphasized that interpreting a calculated dimension as the number of degrees of freedom of a system may be misleading. In that study, Theiler (1995) found that the estimated correlation dimension and Lyapunov exponent were essentially the same for the original data and the surrogate datasets, created by shuffling the phases of the original dataset and thereby ensuring that no dynamic correlation was present from one spike-and-wave pattern to another. With these caveats in mind, Lehnertz and Elger (1995), in their study published the same year as Theiler's analysis, were careful to point out that they were interested only in relative dimension changes over time, and were not considering the dimension estimates to represent absolute degrees of freedom of the system. In 1998, they reported a marked drop in estimated dimension as long as several minutes before seizures that persisted until seizure offset (Lehnertz and Elger, 1998).

Another consideration regarding correlation dimension is whether time series from individual electrodes should be treated separately, reconstructing by time lags alone, or with other channels, forming multichannel reconstructions based on time lag and spatial position. The majority of applications have used separate channels, despite the conclusion of Lachaux et al. (1997),

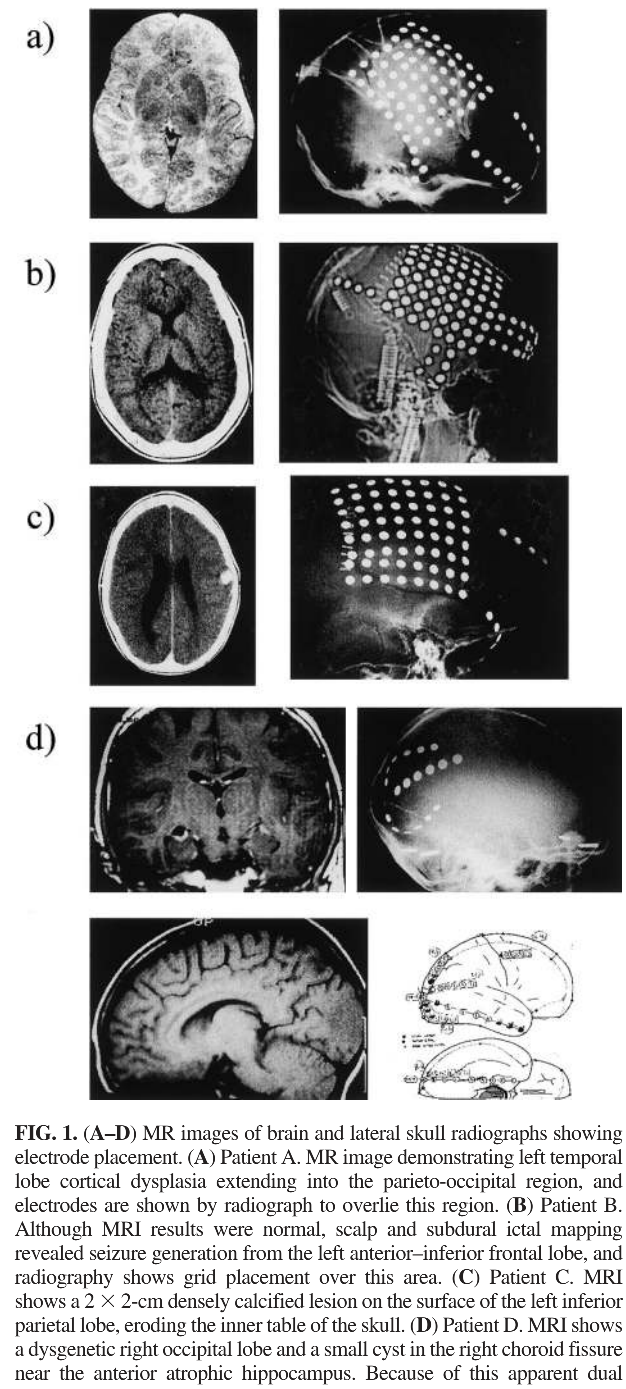

FIG. 1. (**A–D**) MR images of brain and lateral skull radiographs showing electrode placement. (**A**) Patient A. MR image demonstrating left temporal lobe cortical dysplasia extending into the parieto-occipital region, and electrodes are shown by radiograph to overlie this region. (**B**) Patient B. Although MRI results were normal, scalp and subdural ictal mapping revealed seizure generation from the left anterior–inferior frontal lobe, and radiography shows grid placement over this area. (**C**) Patient C. MRI shows a 2 × 2-cm densely calcified lesion on the surface of the left inferior parietal lobe, eroding the inner table of the skull. (**D**) Patient D. MRI shows a dysgenetic right occipital lobe and a small cyst in the right choroid fissure near the anterior atrophic hippocampus. Because of this apparent dual pathology, a single long-depth electrode was placed to record simultaneously from both areas, running from the occipital lobe to the anterior hippocampus.

based on simulated EEG data, that single channels did not do as well as the multichannel method in quantifying spatially extended dynamics. Lerner (1996) articulated another central issue of EEG analysis that transcended estimation of dimension when he stated, "The fundamental problem [leading to poor reproducibility of results] lies in the fact that the time series associated with the EEG are not stationary over periods of sufficient length to permit reliable estimation of the quantities of interest. Indeed, the most interesting feature of the EEG is its nonstationary character."

MUTUAL PREDICTION

Nonlinear systems may synchronize in complex ways that require methods designed specifically for their detection (Pecora et al., 1995; Rulkov et al., 1995). To characterize nonlinear dynamic interdependence between two neuronal systems, Schiff et al. (1996) derived a method based on mutual nonlinear prediction that they applied to spinal cord motoneurons. This method defines the nonlinear predictability of each system based on knowledge about the other system, and it provides information on the directionality of the coupling. This is done by using time-delay reconstructions of two simultaneously sampled time series. Similar states found in a small neighborhood in one reconstruction are checked to determine whether they correspond to similar states in the second reconstruction and to what degree. This method of mutual prediction has been applied to intracranial EEGs of patients with medial temporal lobe epilepsy by Le Van Quyen et al. (1998), and their results indicated a marked difference between the degree of

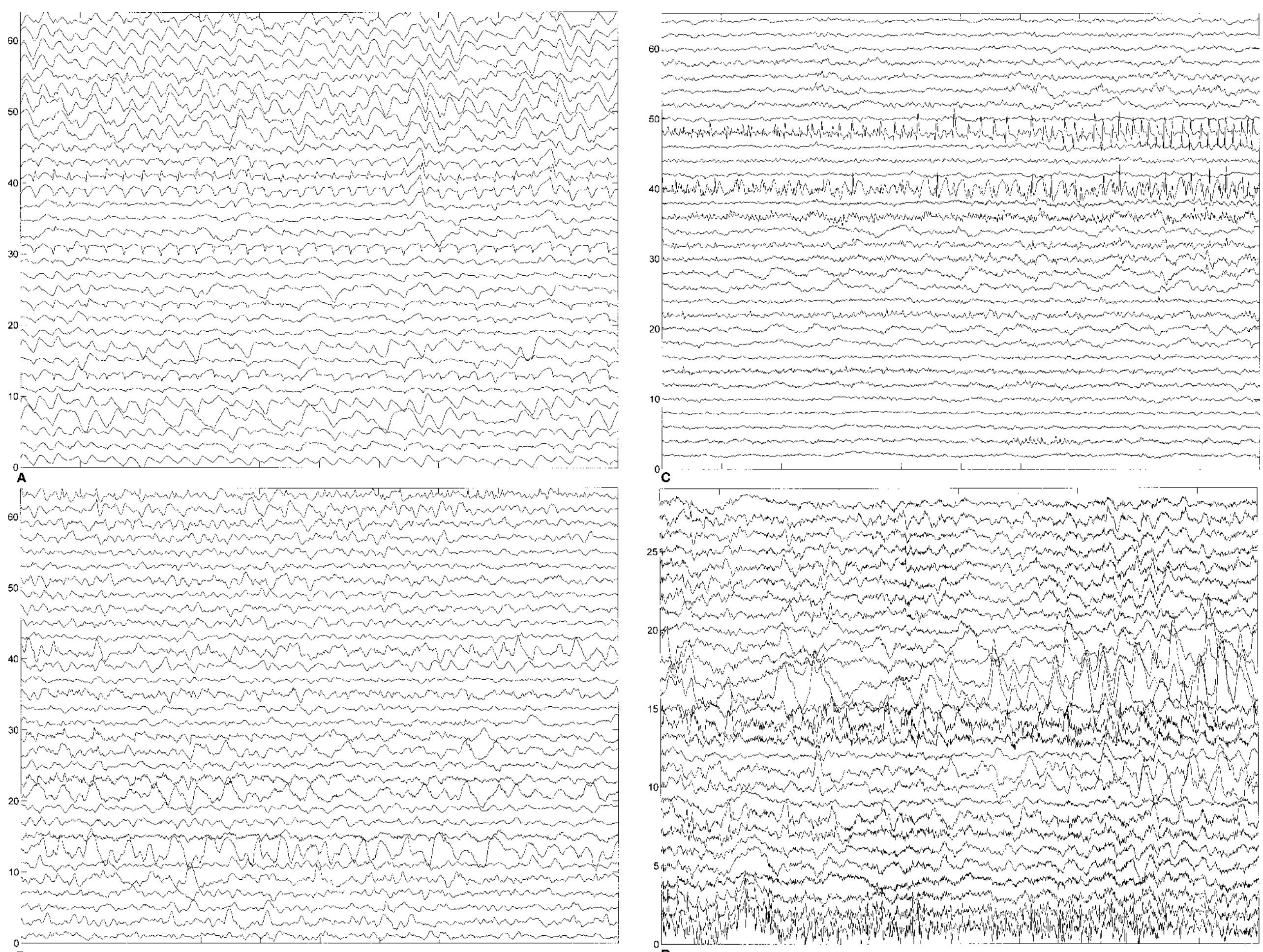

FIG. 2. Samples of raw data from all four patients for three 10-second windows. Every other recording channel is plotted. Note the variability between patients with respect to the number of channels involved in the seizure and the apparent "rhythmicity" of fully developed seizure activity. This heterogeneous set of patients was chosen for comparison of the methods when applied to a range of seizure types.

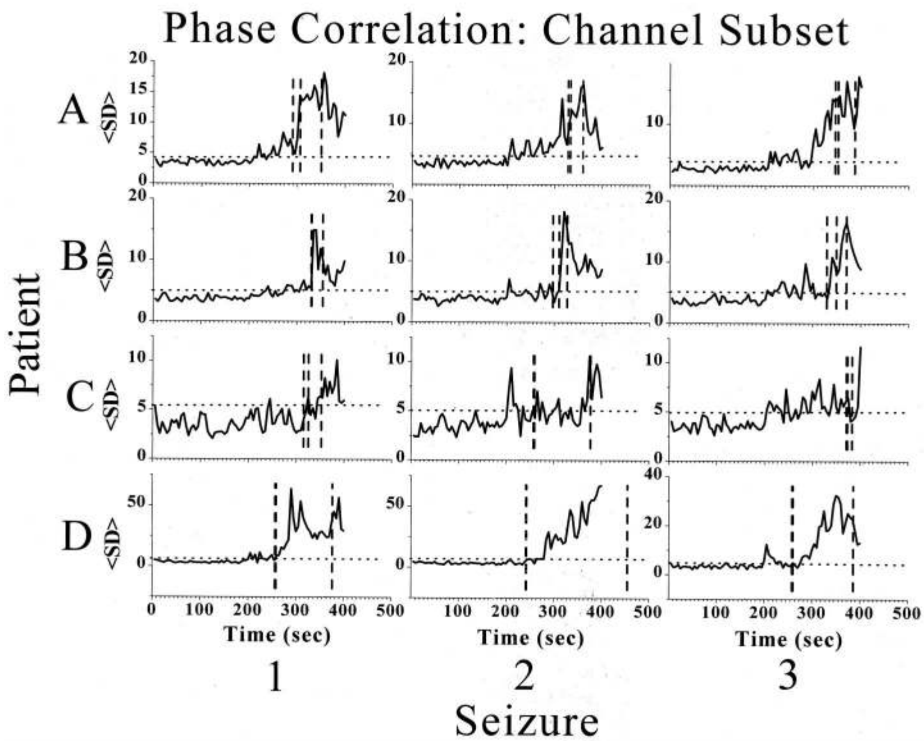

FIG. 3. Average standard deviations from baseline mean of phase analysis for all 12 seizures using the top 10% of channels.

linear interaction measured by the cross-correlation coefficient (which was low) and the degree of nonlinear interaction measured by mutual prediction (which was high) at seizure onset.

These seven methods (power spectral density, cross-correlation, principal components analysis, wavelet packet analysis, phase analysis, correlation dimension, and mutual prediction) were applied as described elsewhere (Jerger et al., 2001) to EEG recordings from subdural and depth electrodes from four children with medically intractable epilepsy during presurgical evaluation (Fig. 1). Three of the children had lesional epilepsy arising from neocortical or hippocampal structures as defined by MRI and confirmed by pathology at the time of resection. One showed glioses by pathology only (normal MRI). After surgical removal of the electrographic seizure focus, each patient either remained seizure free or experienced markedly reduced seizure frequency and severity.

Raw data were bandpass filtered between 0.5 to 30 Hz and referenced externally. The data were segmented into 10-second half-overlapping blocks (2,000 data points per window). Samples of raw data from all four patients for three 10-second windows are displayed in Fig. 2 to give a qualitative sense of how the heterogeneity of seizure origin between patients was reflected in the EEG. The state of all patients before and during seizure onset was confirmed as awake and alert from videotapes recorded simultaneously with the EEG. Note the variability between patients with respect to the number of channels involved in the seizure and the apparent "rhythmicity" of seizure activity. One of the questions asked by the study of Jerger et al. (2001) was whether these differences would be reflected in differential performance of each of the seven methods, and whether a particular method could be best suited to certain seizure characteristics.

For the purpose of comparison across methods, results from each of the seven methods are expressed in numbers of standard deviations. The mean and standard deviation of each method's values during a baseline period with no evidence of seizure activity were calculated for each seizure. Results from all methods were normalized by these values to give the number of standard deviations from the baseline mean for each channel. Results for channels with the top 10% of values were averaged. The maximum value of this average during the baseline period was used as a threshold value, and the first time this value was exceeded was recorded for each seizure.

The average number of standard deviations from the

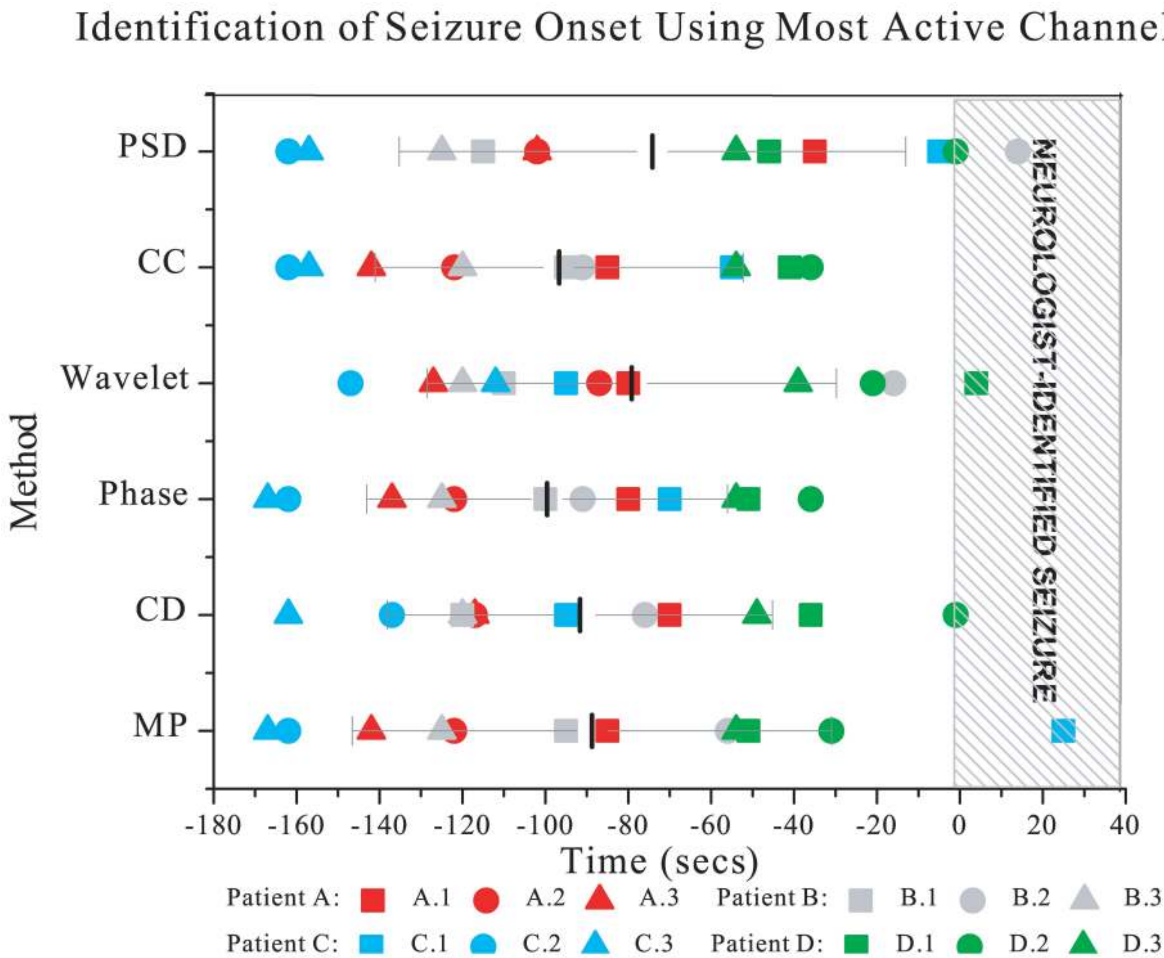

FIG. 4. Difference between threshold crossing time and the neurologist's judgment of electrographic seizure onset. Results for all 12 seizures are shown for each method, with one color corresponding to each patient, and one shape corresponding to the seizure number. One standard deviation is indicated by the horizontal bar, with the vertical bar at its center indicating the mean result over all seizures for that method. The vertical gray line at 0 second corresponds to the time given by the neurologist as electrographic seizure onset. This time preceded clinical seizure onset by an average of 25 seconds.

baseline mean over time for all seizures and all channels is shown in Fig. 3. A neurologist (S.W.) identified three times for each of the 12 seizures using only the electrographic record: (1) initial ictal EEG changes, from here on referred to as the "time of seizure onset"; (2) the beginning of "rhythmic" ictal activity; and (3) seizure cessation. These times are indicated by the dashed vertical lines in Fig. 3. For these 12 seizures, the average amount of time by which the threshold crossing preceded the first vertical line (seizure onset) was 105 seconds.

Fig. 4 shows the differences between threshold crossing times and neurologist-determined seizure onset times for all methods and all seizures, with one color corresponding to each patient. Addressing our earlier question of whether particular methods are best suited to a particular patient, there is a tendency for results from a particular patient to be grouped together across methods (giving the appearance of longitudinal colored stripes), suggesting that factors specific to individual patients play an important role in determining how early a seizure may be detected, and in many cases this variability between individuals may have more of an influence on the predictability of seizures than the seizure detection method chosen.

These seven methods were successful in detecting changes leading to a seizure as long as 2.5 minutes before the first visual evidence of electrographic seizure onset was noted by the neurologist. It should be emphasized that the time most frequently reported in the literature as that of seizure onset is the time rhythmic activity is evident in the EEG. Here we have used instead the time the first epileptiform changes were noted by the neurologist, which always preceded rhythmic activity by an average of 25 seconds. Thus, the average lead time given by phase correlation, before clinical onset, is more than 2 minutes.

Interestingly, the threshold crossing times given by the linear methods often occurred earlier than or at the same time as some of the nonlinear methods. We found this surprising because many behaviors of neurons are known to follow nonlinear dynamics, from all-or-none firing to communication through synaptic transmission. Thus, one may expect that there is always underlying nonlinear behavior in EEG that is not fully characterized by linear tools—activity that should be reflected in our nonlinear measures. It is likely that the EEG signals are so complex that nonlinear reconstruction methods may not capture the dynamics accurately. Nonlinear tools are often designed to reveal structure from low-dimensional nonlinear systems. Faced with a truly complex system (with many degrees of freedom), they may fare worse than a linear analysis, as seen for correlation dimension and mutual prediction in these results. In addition, the method of obtaining the initial measurement may exclude relevant information. Using higher than standard sample frequencies and electrode placement density as well as using distant recording sites to improve the resolution and widen the spatial range of sampling may lead to reconstructions that better reflect the true system dynamics.

Linear methods also have weaknesses. For example, a limitation of PCA is that it is restricted to defining directions that are orthogonal to each other. In their analysis of functional MRI, McKeown et al. (1998) found that their method based on Bell and Sejnowski's (1995) independent component analysis algorithm, which allows for nonorthogonal directions as well as a related fourth-order decomposition technique (Comon, 1994), was superior to PCA in determining the spatial and temporal extent of task-related activation. A method for performing a nonlinear form of PCA has recently been proposed (Scholkopf et al., 1998) that involves the use of integral operator kernel functions. An open question remains as to how to choose the ideal kernel for a particular application.

The substantial differences between patients appeared to play a greater role in seizure predictability than the method selected. This result may be due in part to our choice not to "individualize" parameters. Had we chosen settings most appropriate for a particular patient, we may have found particular methods to be patient specific. In any case, it is likely that results could be improved by optimizing parameters for a particular patient, and by "training" the algorithm on known seizures before presenting it with test data.

In conclusion, all seven methods were successful in indicating seizure onset before the neurologist for all but a few seizures—most of them 1 to 3 minutes in advance of electrographic onset. Because clinical seizure onset occurred an average of 25 seconds after electrographic onset, the lead time before clinical onset given by these methods (at $p < 0.05$) was even longer and may prove to be sufficient for incorporation into future control devices. Nevertheless, these procedures should be applied to recordings spanning many minutes or hours to see how they fare when blind to whether a seizure will occur. Only with such validation can conclusions regarding their usefulness for true seizure prediction be reached. Finally, although we did not uncover significant differences between linear and nonlinear methods, our analysis of phase performed slightly better than the other methods, which may reflect its sensitivity in detecting weakly coupled nonlinear systems.

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