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Multivariate linear discrimination of seizures

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Abstract

Objective: To discriminate seizures from interictal dynamics based on multivariate synchrony measures, and to identify dynamics of a pre-seizure state.

Methods: A linear discriminator was constructed from two different measures of synchronization: cross-correlation and phase synchronization. We applied this discriminator to a sequence of seizures recorded from the intracranial EEG of a patient monitored over 6 days.

Results: Surprisingly, we found that this bivariate measure of synchronization was not a reliable seizure discriminator for 7 of 9 seizures. Furthermore, the method did not appear to reliably detect a pre-seizure state. An association between anti-convulsant dosage, frequency of clinical seizures, and discriminator performance was noted.

Conclusions: Using a bivariate measure of synchronization failed to reliably differentiate seizures from non-seizure periods in these data, nor did such methods show reliable detection of a synchronous pre-seizure state. The non-stationary variables of decreasing antiepileptic medication (without available serum concentration measurements), and concomitant increasing seizure frequency contributed to the difficulties in validating a seizure prediction tool on such data.

Significance: The finding that these seizures were not a simple reflection of increasing synchronization in the EEG has important implications. The non-stationary characteristics of human post-implantation intracranial EEG is an inherent limitation of pre-resection data sets.

Keywords: Electroencephalography; EEG; Intracranial; Cross-correlation; Phase synchrony; Prediction

1. Introduction

EEG is a complex signal. As a crude measure of electrical activity within the brain, we are aware of no single measure that adequately captures the nature of EEG dynamics or the dynamics of the underlying brain processes. Although there have been extensive univariate analyses of EEG and seizure dynamics, much less exploration of the role of formal multivariate analysis and discrimination has been attempted. In principle, multiple independent measures of relevant brain and seizure dynamics should help to discriminate interictal and ictal states with higher accuracy than any single measure.

Seizures have long been postulated to be a manifestation of excessive synchronization, and the earliest reference to 'hypersynchronization' that we are aware of was by Penfield and Jasper (1954). Since then, the presumption that seizures are a manifestation of synchronization has become pervasive (Kandel et al., 1991). Indeed, there have been multiple recent findings consistent with the possibility that a measure of synchronization might indicate changes in EEG dynamics prior to seizure onsets (Jerger et al., 2001; Lehnertz and Elger, 1995, 1998; Lerner, 1996; le Van Quyen et al., 1998, 1999; Lopes da Silva et al., 1989; Mormann et al., 2000; Quian Quiroga et al., 2002).

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Multivariate analysis of data has become highly refined in the 20th century (Anderson, 1984; Johnson and Wichern, 1998). In multivariate analysis, independent measures of data can be shown to be more sensitive than univariate discriminators. Furthermore, for correlated variables, a formal multivariate approach can be far more accurate in classifying data than multiple independent comparisons.

We here follow the approach of Flury (1997), and construct a linear discriminator based on measures of cross-correlation and phase synchronization during seizure and non-seizure periods. If seizures were a manifestation of increased synchronization, we hypothesized that a pre-seizure state could consist of a partial increase in synchronization bridging the interictal and seizure periods.

2. Methods

Data set B from the Department of Epileptology, University of Bonn, was visually inspected in its entirety by a Board Certified Neurologist and Clinical Neurophysiologist (SLW). This data set comprised intracranial recordings from a patient monitored over 6 days. Unequivocal seizure onsets and offsets were identified from the EEG as well as the earliest visually evident electrographic changes. Groups of channels demonstrating similar activity were identified as clusters. Clusters of electrodes included the left posterior hippocampal depth electrode (channels 35–38) from which the earliest EEG changes were noted, the left anterior hippocampal depth electrode (channels 31–33), the site of consistent electrographic seizure onset, and the contralateral homologous hippocampal depth and contralateral temporal neocortical electrodes. The choice of anterior and posterior hippocampal electrode clusters was supported by Independent Component Analysis (ICA) which tended to group these two electrode clusters into similar components (Hyvärinen and Oja, 1997).

We screened the multivariate synchronization measure for ipsilateral and contralateral electrode pairings, and found that the earliest changes in the measure appeared to occur between the anterior and posterior hippocampal electrodes ipsilateral to the seizure focus. We here report a detailed discrimination analysis between these electrodes.

Raw data was analyzed in consecutive 10 s windows (2000 datapoints at 200 Hz sampling rate) with 1 s window overlap. The mean voltage within each data window was removed and the voltages divided by the standard deviation to normalize the values.

For each data window, cross-correlation and phase synchronization (Tass et al., 1998) was calculated for each electrode pair. To characterize the cross-correlation and phase synchronization between each pair of electrode clusters (anterior hippocampus vs. posterior hippocampus), a single value for each window was obtained by averaging across all combinations of intercluster channel pairs (with one channel belonging to each cluster).

A linear multivariate discriminator was then constructed to classify data windows as either seizure or non-seizure. The discriminator was 'trained' using training samples selected by using the values for all seizure windows between unequivocal seizure onsets and offsets, and an equal number of randomly selected non-seizure windows. Non-seizure windows were selected from the 2 h period ending 1 h before the identified seizure period, so as not to include the immediate pre-ictal period. We required that this 2 h period start at least 1 h after a previous seizure to exclude the post-ictal period (a total of 4 h between seizures was required). A bootstrap procedure was employed to determine the significance of the discriminator results. In order to deal with non-stationarities in the data, the discriminator was recalculated after each subsequent seizure.

Full details of the Methods are given in the Appendix of this paper.

3. Results

The probability that the bivariate synchrony discriminator classified the training sets correctly varied from 100% accuracy (seizures 1 and 7), to as low as 24% (seizure 9). Quite unexpectedly, this synchrony discriminator failed to achieve over 95% accuracy in classification in 7 of 9 seizures (Table 1).

Fig. 1 shows the number of discriminations (4 of 5 consecutive threshold crossings) for the entire time series. Before 8 seizures (seizures 3, 5, 6, 7, 8, 10, 11, and 12) the frequency of discriminations was very high. One might be tempted to interpret these periods of frequent discriminations as a 'preseizure state'.

By constructing the training sets comparing 2 h before the seizure versus the seizure, excluding the immediate 1 h pre-seizure, the discriminator was ideally suited to pick up subtle synchrony changes within the pre-seizure hour. Although such activity might be ascribed to the hour before

Table 1
Performance of 100 discriminators for each seizure

Seizure number	Mean P	% Discriminators with $P<0.05$
1	0.0018	100
2	0.1030	45
3	0.0138	91
4	0.0855	56
5	0.0291	84
7	0.0010	100
9	0.2713	24
11	0.0500	72
12	0.0059	88

Mean bootstrap estimate of probability (P) of falsely rejecting the null hypothesis is the fraction of resamplings whose standard distance exceeds the distance between seizure and non-seizure data (see Appendix).

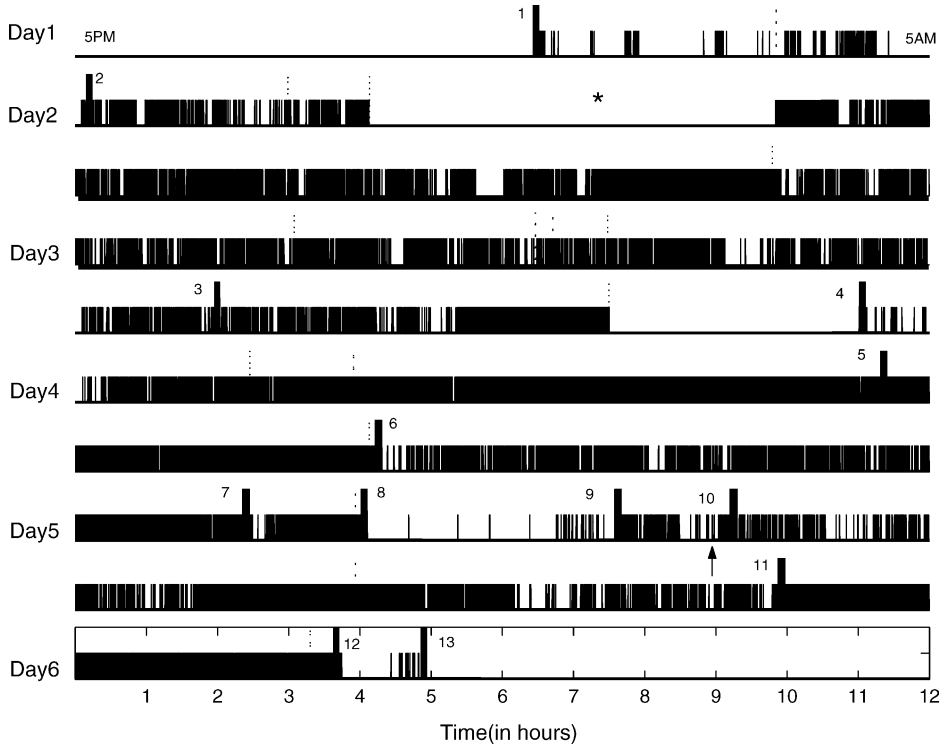

Fig. 1. Entire sequence of seizures over 6 days, indicated by numbered tall bars, and the significant discriminations (4 out of 5 consecutive threshold crossings) indicated by short bars (further details on discriminations are found in Appendix). Recordings were interrupted for media changes at the dotted lines. Asterisk (*) indicates recording gap. Medication was restarted at the up-arrow.

seizures 10 and 13, no such consistent pattern is observed before other seizures among the full set of data from Fig. 1.

The seizure frequency gradually increased each day through day 5, and the frequency of discriminations peaked on day 4.

The frequency of threshold crossings is shown more clearly in Fig. 2 (third panel). In the top two panels of Fig. 2 are shown the daily seizure count, and the cumulative daily oral anticonvulsant dosages. The progressive discrimination frequency peaked (panel 3) as the medication taper was completed by day 4, when all medication was stopped. Medication was resumed (with the addition of a new medication, clobazam) at 2 pm on day 5 (up-arrow, Fig. 1). The reflection of medication taper and seizure frequency seen in discrimination frequency was not reflected in the univariate cross-correlation and phase synchronization averages shown in the bottom two panels of Fig. 2. Thus medication dosage and seizure frequency appeared to contribute to significant non-stationarity of the data throughout the 6 days of recording.

4. Discussion

Using a bivariate measure of synchronization failed to reliably differentiate seizures from non-seizure periods in these data, nor did such methods show reliable detection of a synchronous pre-seizure state.

There are several possibilities to account for such discriminator behavior. In using a measure of synchronization to characterize seizures, we make the assumption that a pre-seizure state would reflect a subtle development of the same dynamics that characterize the upcoming seizure. One hopes that by using a sensitive quantitative measure and discriminator, that such detection of a pre-seizure state can be made in advance of the unequivocal electrographic seizure onset or of the clinical manifestations of the seizure.

One possibility is that the discriminations as seen in Fig. 1 are nearly all reflective of a pre-seizure state. Certainly, each flurry of discriminations was followed within minutes or hours by a seizure. Unfortunately, we do not now have the physiological or dynamical understanding to delineate a pre-seizure state.

Another possibility is that seizures, and a possible pre-seizure state, are not reflected in a simple increase or decrease in a synchronization measure. If this were true, then the frequent discriminations shown in Fig. 1 would not have a straightforward relationship to impending seizures. One reason for such complexity is non-stationarities in the data.

There were several non-stationary features of this data set that are typical of patients monitored following intracranial implantation of electrodes for seizure localization. Time is at a premium once electrodes are implanted, since the risks of infection, electrode breakage, and costs all increase with time. Consequently, antiepileptic medication

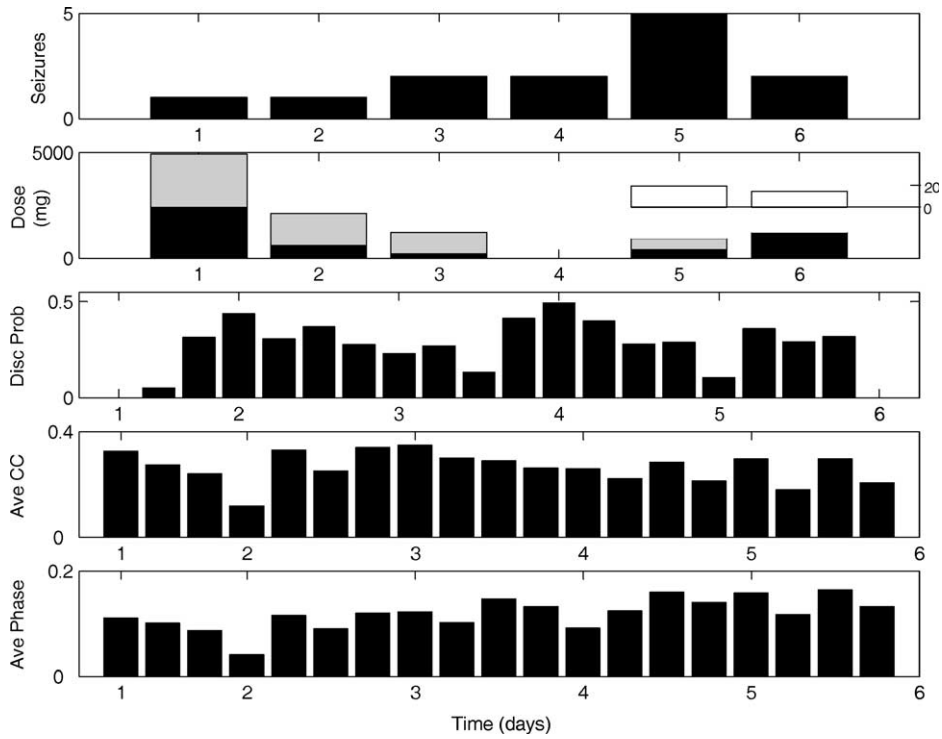

Fig. 2. Cumulative daily seizure count is shown in the top panel, and cumulative daily anticonvulsant dosages are shown in the second panel (grey indicates lamotrigine, black indicates carbamazepine, and white indicates clobazam, shown with its own scale since dosages are much smaller for this medication). The third panel shows the probability (average number) of bivariate discriminations in 6 h periods. The bottom two panels show 6 h averages of the univariate cross-correlation and phase synchronization indices, respectively.

is rapidly tapered in the days following surgery (Yen et al., 2001). Such a practice encourages the rapid emergence of seizures in most chronically epileptic subjects, but the EEG dynamics are then recorded during a background of rapidly decreasing drug levels in the brain. Fig. 2 demonstrates that the performance of the discriminator appeared to correlate with changing antiepileptic medication dose. Such a feature in the dynamics would render the discrimination threshold a continually moving target, and may have accounted for some of the difficulty in applying our measure.

As a consequence of seizures in the setting of decreasing medication levels, such patients also frequently express an increasing frequency of seizures, resulting in increased clustering of seizures such as seen in these data (Figs. 1 and 2). The presence of frequent seizures and seizure clusters may indicate that the brain would not have had adequate time to recover dynamically to its normal interictal state before the next seizure occurs. This is another source of non-stationarity that may have contributed to the failure of our discriminator.

Unfortunately, non-stationarities due to recent surgical trauma, decreasing drug levels, and increasing seizure frequency, are largely inherent in data sets collected from patients implanted with electrodes for seizure localization. In data sets such as the one analyzed here, the concept of a ‘preseizure’ state becomes difficult—the findings from Fig. 1 may indeed have revealed that the patient was in a continual pre-ictal state. Without an independent dynamical definition of a pre-ictal state (and ictal state for that matter), there will remain no way to validate a seizure predictor in such data. The ideal data set required to validate a seizure predictor would be from a long term chronically implanted patient, with stable anticonvulsant medication levels, going about the activities of daily living and experiencing a ‘normal’ seizure frequency. Since such data sets are not available, non-stationarity renders validation of a prediction tool rather problematic.

One of the fascinating biological features of this study was the finding that synchronization was not able to reliably differentiate seizure from non-seizure training periods in 7/9 seizures (Table 1). Note that the discriminator did not differentiate between an increase or decrease in synchrony—only whether the synchronization consistently differed between seizure and interictal periods in the training sets. One way to account for our findings would be if synchronization followed a complex course during the seizure period.

Experimental evidence that seizures might contain both desynchronous and synchronous phases has recently been observed from dual intracellular recordings (Netoff and Schiff, 2002). Such findings are fully consistent with previous observations of multiple single neurons in vitro (Perez Velazquez and Carlen, 1999), and some of the rare multiunit recordings from human seizures in vivo (see, e.g. Figs. 7–9 from Wyler et al., 1982). Such observations are also consistent with a growing body of theoretical literature

demonstrating that the maintenance of persistent activity in a neuronal network (Gutkin et al., 2001), or the activity of inhomogenous networks as coupling strength is increased (Golomb and Hansel, 2000), may all require asynchrony. Although the link between single neuron interactions and EEG is not clear, our findings are consistent with the possibility that the seizures from this data set were not characterized by a simple increase in synchronization. These findings suggest that a more successful seizure and pre-seizure discrimination strategy may require a more detailed analysis of the time course of the dynamical properties of seizures.

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Appendix

For each data window, cross-correlation at zero delay, $C(0)$, was calculated from the normalized electrode pair data x_1 and x_2 as $C(0) = (1/N)\sum_{i=1}^{N} x_1(i)x_2(i)$ where N is the number of data points (2000).

For each time window phase was assigned by calculating the Hilbert transform, $\hat{x}$, on each time series x as $\hat{x}(t) = (1/N)\,\mathrm{Im}[2\sum_{k=1}^{N/2} f(k/N)\mathrm{e}^{-\mathrm{i}2\pi kt/N}]$ where Im[ ] indicates the imaginary part, and $f(k/N)$ is the Fourier transform of $x(t)$. The values of the Hilbert transform supplied the imaginary part of the Gabor analytic signal, $x(t) + \mathrm{i}\hat{x}(t)$, and the phase, $\varphi(t)$, was assigned as $\varphi(t) = \arctan \hat{x}(t)/x(t)$. Phase synchronization between two electrodes was determined as follows. Two sequences of phase angles, $\varphi_1(t)$ and $\varphi_2(t)$ for electrodes x_1 and x_2, respectively, were subtracted to obtain a sequence of phase angle differences, $\varphi_1(t) - \varphi_2(t)$, with length equal to the original data window (2000 datapoints). Such a sequence reflects the strength of one to one phase locking (Tass et al., 1998). The first and last 1 s (200 values) were discarded from each data window to minimize phase calculation edge artifacts (Mormann et al., 2000). We have avoided narrow band filtering of data prior to Hilbert transformation (Netoff and Schiff, 2002).

For each data window, we therefore calculated one value of cross-correlation at zero phase lag, and 1600 values (over 8 s) of phase difference. Because windows were overlapped by 1 s, a phase difference was assigned for each time point in the data. We reduced this set of phase difference values to one measure per window by creating a histogram of values with $h = 20$ bins, and quantifying the deviation from uniform (randomly distributed) phase differences using a measure of entropy, s, similar to Tass et al. (1998), where $s = -(1/h)\sum_{j=1}^{h} P(j)\log(P(j))$, and the probabilities, $P(j)$, were estimated from $P(j) = m(j)/1600$, where $m(j)$ represents the number of values within each bin j. The values of s were normalized against the maximal possible entropy, $S_{\max} = \log N$, to give $S = (S_{\max} - s)/S_{\max}$. This entropy S yielded a numerical value between 0 (complete asynchrony, where all phase differences were equally probable), and 1 (perfect synchrony where all phase differences fell within one bin).

To characterize the cross-correlation and phase synchronization between each pair of electrode clusters (anterior hippocampus vs. posterior hippocampus), a single value for each window was obtained by averaging across all combinations of intercluster channel pairs (with one channel belonging to each cluster).

A linear multivariate discriminator was then constructed to classify data windows as either seizure or non-seizure. Average cross-correlation, $\bar{C}(0)$, and phase synchronization, $\bar{S}$ values for each of the windows were combined into a vector $\boldsymbol{X}$

$$\boldsymbol{X} = \begin{pmatrix} \bar{C}(0) \\ \bar{S} \end{pmatrix}$$

The training samples were selected by using the values for all seizure windows ($\boldsymbol{X}_1$), between unequivocal onsets and offsets, and an equal number of randomly selected non-seizure windows ($\boldsymbol{X}_2$). Non-seizure windows were selected from the 2 h period ending 1 h before the identified seizure period, so as not to include the immediate pre-ictal period. We required that this 2 h period start at least 1 h after a previous seizure to exclude the post-ictal period.

Discriminators were obtained by first computing the bivariate mean, $\bar{\boldsymbol{X}}$, and covariance matrix, $\boldsymbol{\Psi}_i$ for seizure samples ($\bar{\boldsymbol{X}}_1$ and $\boldsymbol{\Psi}_1$) and non-seizure samples ($\bar{\boldsymbol{X}}_2$ and $\boldsymbol{\Psi}_2$). The pooled covariance matrix, $\boldsymbol{\Psi}$, was then calculated as

$$\boldsymbol{\Psi} = \frac{1}{N_1 + N_2 - 2}((N_1 - 1)\cdot\boldsymbol{\Psi}_1 + (N_2 - 1)\cdot\boldsymbol{\Psi}_2)$$

where N_1 and N_2 are the number of seizure and non-seizure samples, respectively. The inverse of this matrix, $\boldsymbol{\Psi}^{-1}$, multiplied by the vector of mean differences between seizure and non-seizure classes ($\boldsymbol{d} = \bar{\boldsymbol{X}}_1 - \bar{\boldsymbol{X}}_2$), yields the coefficients of the linear discriminant function

$$\boldsymbol{b} = \boldsymbol{\Psi}^{-1}\boldsymbol{d} = \begin{pmatrix} b_1 \\ b_2 \end{pmatrix}$$

where b_1 and b_2 are the coefficients of the cross-correlation and phase synchronization discriminant variables, respectively. The univariate linear discriminant function, v, can then be expressed as (Flury, 1997)

$$v = \boldsymbol{b}^{\mathrm{T}}\cdot\boldsymbol{X} = b_1x_1 + b_2x_2$$

where T indicates transpose.

A bootstrap procedure that did not require that the data were normally distributed was employed to determine the significance of the discriminator results. The null hypothesis is that the standard distance, $\sqrt{\boldsymbol{d}^{\mathrm{T}}\boldsymbol{b}}$, between the values of $\boldsymbol{X}_1$ from seizure windows and the values of $\boldsymbol{X}_2$ from non-seizure

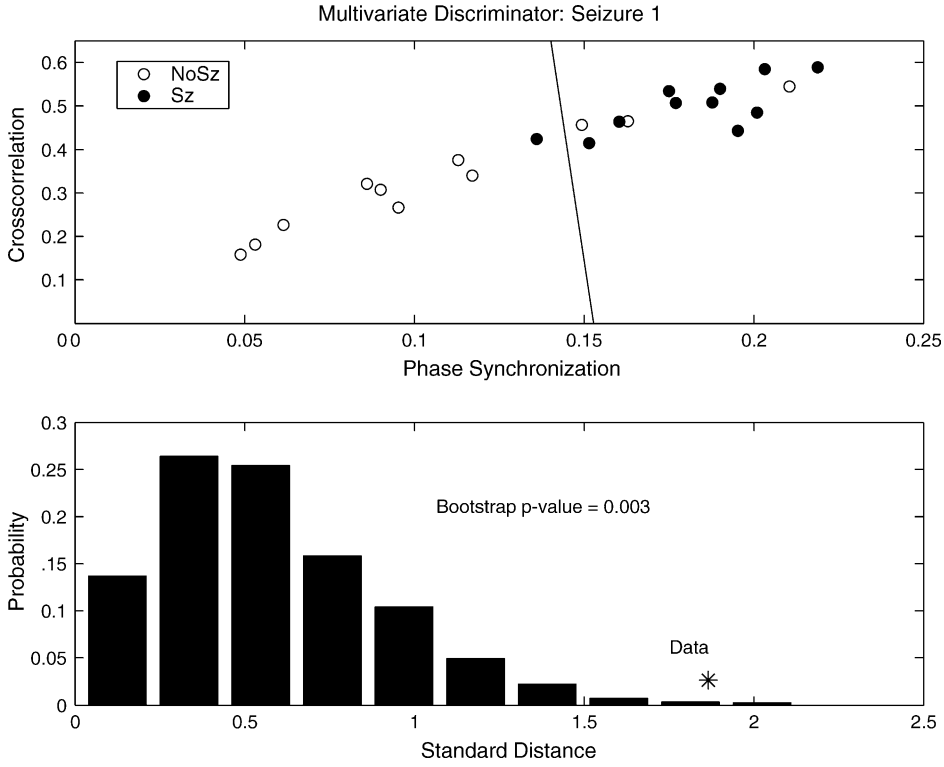

Fig. A1. A single linear multivariate discriminator of cross-correlation and phase synchronization successfully discriminates ($P=0.003$) seizure (closed circles, ●) and non-seizure (open circles, ○) samples for seizure 1 of this data set (see Appendix for details). In the top panel, the black line shows the optimal linear discriminator for these data. In the bottom panel, are shown the results of the bootstrap procedure used to evaluate the significance of the discrimination results in the top panel. The assignment of the data values to 'seizure' or 'non-seizure' was randomized, and the standard distance was recalculated. It is shown that the standard distance for the actual seizure and non-seizure data (asterisk, *) are rarely exceeded by the resampled results, and are thus very unlikely to be due to chance.

windows were due to chance. Rejecting the null hypothesis requires us to demonstrate that the particular arrangement of values into $\boldsymbol{X}_1$ and $\boldsymbol{X}_2$ is unusual. We therefore performed 1000 random resamplings of the training values of $\boldsymbol{X}$ reassigning the values to seizure and non-seizure groups. The significance of falsely rejecting the null hypothesis, P, is therefore equal to the fraction of the 1000 resamplings for which the standard distance between the bootstrap groups exceeded the standard distance between the original seizure and non-seizure groups (Fig. A1). For each seizure, 100 discriminators were constructed by selecting the seizure and a different randomly selected set of non-seizure windows (from applicable non-seizure windows as specified in Section 2), and the significance of the discrimination reevaluated by the bootstrap procedure. The percentage of these 100 discriminators that successfully classified seizure versus non-seizure ($P<0.05$) are reported in Table 1. The slope and intercept from the successful linear discriminators (each is equivalent to a straight line as in Fig. A1) for each seizure were then averaged to obtain the discriminator to use until the next seizure occurred.

In order to deal with non-stationarities in the data, the averaged discriminator was recalculated after each subsequent seizure. A significant discrimination was said to have occurred if the discriminator classified 4 out of 5 consecutive windows as significant (for independent events, the binomial probability of such an occurrence would be <0.0001). Seizures were excluded from being used as a training set if another seizure occurred within 4 h prior to it. Seizures 6, 8, 10, and 13 were excluded on this basis, leaving 9 seizures as training sets.

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