

Neuronal spatiotemporal pattern discrimination: The dynamical evolution of seizures

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We developed a modern numerical approach to the multivariate linear discrimination of Fisher from 1936 based upon singular value decomposition that is sufficiently stable to permit widespread application to spatiotemporal neuronal patterns. We demonstrate this approach on an old problem in neuroscience—whether seizures have distinct dynamical states as they evolve with time. A practical result was the first demonstration that human seizures have distinct initiation and termination dynamics, an important characterization as we seek to better understand how seizures start and stop. Our approach is broadly applicable to a wide variety of neuronal data, from multi-channel EEG or MEG, to sequentially acquired optical imaging data or fMRI.

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Introduction

Multivariate canonical discrimination was invented by Fisher in 1936 in order to quantify the static taxonomic classification of plant species (Fisher, 1936). The method seeks to discriminate between species based on weighting different measurements (such as petal length and width) such that the aggregate data from different species are maximally separated. Modern implementations of this technique (Flury, 1997) can be numerically unstable when applied to dynamical measures of EEG data, when common measures of signal frequency or correlation may at times have very small absolute numerical values further

confounded by noise and measurement error. We invent a novel approach to the numerical solution of multivariate discrimination, which is consistent with Fisher's original results, yet permits an application to the analysis of neuronal electrical activity. Our approach can be used in many other settings (EEG, MEG, Optical Imaging, fMRI).

Although we frequently define seizures as monolithically distinct dynamical entities – ictal as opposed to interictal – it has long been clear that the characteristics of seizures can change distinctively during an event. Many seizures behaviorally change from focal to generalized activity, or from tonic to clonic muscle contractions, and there are characteristic EEG changes that accompany such transitions. Early work by Kandel and Spencer (1961) revealed at least 3 stages of hippocampal seizures in fornix deafferented cats. Studying EEG, extracellular local field potentials, and single intracellular recordings from untyped cells from cat cortex following topical penicillin application, Matsumoto and Marsan (1964) suggested qualitative segmentation of seizures into 'onset, development course and end'. Ayala et al. (1970) recorded from similar seizures and demonstrated (see their Fig. 1) an onset phase of seizures distinct from a middle tonic and terminal clonic phase. Previous work quantifying the segmentation of seizures focused on the symbolic similarities (or dissimilarities) between seizures (Wendling et al., 1996, 1999; Wu and Gotman, 1998), yet their findings illustrated that EEG signals, from single channels and in aggregate, changed during the course of a seizure. Today, we have still never defined dynamically a seizure 'onset' stage, and such a characterization is essential if we are to distinguish a pre-ictal state from the start of a seizure with better accuracy (Litt et al., 2001). Similarly, identifying a distinct terminal phase of a seizure would be useful in understanding why seizures stop, and how to hasten such termination.

We here apply to our knowledge the first canonical discrimination analysis to search for dynamically distinct stages of

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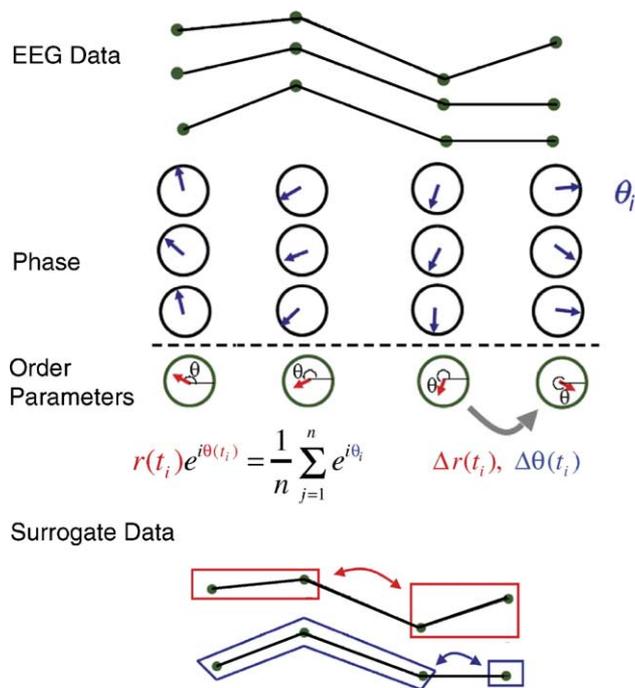


Fig. 1. Schematic of EEG data analysis. Simulated EEG data voltages are shown above for 3 channels with 4 time points each. Following Hilbert transformation and assignment of a phase angle θ_i for each data point, shown as blue vectors, the order parameters of average amplitude, $r(t_i)$ and phase angle $\theta(t_i)$ are determined at each time point t_i . In addition, the differences between average amplitude $\Delta r(t_i)$ and angle $\Delta \theta(t_i)$ within a data window (200 points for each second of data) are used to calculate the variance of the $\Delta r(t_i)$ and $\Delta \theta(t_i)$ that create a measure of phase dispersion. As a multichannel system synchronizes, the average amplitude $r(t_i)$ within a window will increase towards unity, while its amplitude differences $\Delta r(t_i)$ go to zero. Similarly, synchronization among channels will make average angle differences $\Delta \theta(t_i)$ constant. Thus, the variance of both the amplitude differences $\Delta r(t_i)$ and average angle differences $\Delta \theta(t_i)$ will decrease towards zero in the synchronous state. At the bottom of the figure is shown a schematic of our scheme for surrogate data construction for 2 channels of data within a data window (200 points, only 4 shown). For each channel with amplitude data, the time series is cut at a random location within each data window, and the 2 segments created are swapped in location. This cutting and swapping is performed at a different random location for each channel, and the resultant data set subjected to the same correlation analysis as the original data. The randomization and swapping is repeated, and thus an ensemble of results obtained for which local correlations are largely destroyed. For phase data as shown above, the Hilbert transformation is performed on the entire data set. For phase data, the randomizations are performed for phase angle time series within each data window, choosing random times to cut each 200 point time series of phases, and swapping the 2 segments. Again, these surrogate phase ensembles are used to generate new order parameters of average amplitude, $r(t_i)$ and phase angle $\theta(t_i)$ at each time point, as well as their differences $\Delta r(t_i)$ and $\Delta \theta(t_i)$, which are used for comparison with the original data set. Note that these block shufflings used to destroy short term correlations in amplitude and phase data are distinct from the random permutations used to re-label the multivariate points in Figs. 4F and 5F.

epileptic seizures in humans. Applying these techniques to human seizures recorded both from the scalp and intracranially, we find in almost all cases the identification of unique initiation and termination stage dynamics, distinct from the persistent middle phase of seizures.

Methods

Human seizures

All human research was carried out on archived data stripped of patient identifiers. This work was approved as Category 4 Exempt research by the Institutional Review Boards of both the Children's National Medical Center and George Mason University.

Seizure start and stop times were chosen using customary clinical EEG inspection by a Board Certified Neurologist (SLW) and Neurosurgeon (SJS). To fully contain the seizure, the nearest integer second before the seizure onset, and the nearest integer after seizure offset, were selected. We as others (Wu and Gotman, 1998) were extremely reluctant to pre-select which electrodes should be employed for analysis. Our only criteria for exclusion were the presence of significant artifact in the recording channel. For scalp data, 23 channels were used according to the standard 10–20 system. For intracranial recordings, the 4 subjects had 28, 63, 63, and 64 usable channels, respectively.

All data were recorded following analog high pass filtering between 0.1 and 0.3 Hz, and low pass filtering at 100 Hz, prior to digitization at 200 Hz. Before signal processing, data were passed through a 9th order low pass Butterworth filter with a cutoff frequency of 55 Hz in order to prevent 60 Hz power line contamination from affecting our correlation measures. The mean voltage offset of each channel was similarly removed prior to analysis.

Dynamical measures

Six dynamical measures were calculated within each non-overlapping 1 s window of data: total power, total correlation at both zero and arbitrary time lag, phase amplitude coherence, and phase angle and amplitude dispersion. The choice of these six 'features' is rather arbitrary, but our goals were to reflect measures of synchronization from several semi-independent approaches, and in addition the signal power, which is intimately related to changes in epileptic EEG.

Total power was calculated by summing the squared value of each voltage value.

Two measures reflecting total correlation were calculated. Each electrodes' time series, $x_i(t)$, where i indicates channel number, was first-order detrended within each $T = 1$ s window, and then the normalized crosscorrelation function, $c_{i,j}(t)$, was calculated with up to 1/2 s of lag

$$c_{i,j}(\tau) = \frac{\sum_{t=-T/2}^{T/2} x_i(t)x_j(t+\tau)}{\left(\sum_{t=-T/2}^{T/2} (x_i(t))^2\right)^{1/2} \left(\sum_{t=-T/2}^{T/2} (x_j(t))^2\right)^{1/2}}$$

This was performed for all unique channel pairs (i,j), and either the values at zero lag ($\tau = 0$),

$$S_0 = \sum_{\substack{i,j=1 \\ i \neq j}}^n |c_{i,j}(\tau = 0)|$$

or the values larger than twice the estimator of standard deviation (Bartlett, 1946; Box and Jenkins, 1976), $\sigma_{ij}^2(\tau)$,

$$\sigma_{ij}^2(\tau) = \left| \frac{\sum_{\tau=-T/2}^{T/2} c_{i,i}(\tau)c_{j,j}(\tau)}{(T+1-\tau)} \right|,$$

$$S_\tau = \sum_{\substack{i,j=1 \\ i \neq j}}^n \sum_{\tau=-T/2}^{T/2} \left| C_{i,j}(\tau) \right| \theta \left(\left| C_{i,j}(\tau) \right| - 2\sigma_{ij}(\tau) \right)$$

were summed to yield values S_0 or S_τ , respectively (θ is the Heaviside function). Such measures S reflect the total amount of correlation between all channel pairs within the window. Examples of such correlation values are seen in Fig. 3C, where the correlation value at zero lag is the value in the center of the plots, and the values of correlation exceeding twice the standard deviation of the confidence limit are the values exceeding the red error bars at arbitrary lags. Such arbitrary lags will turn out to be crucial to consider when propagation delays are present in a system.

Phase was calculated in broad-band from Hilbert transformation of each full time series from each electrode (at this stage without regard to the smaller 1 s windows). The Hilbert transform is defined as $h(t) = \frac{1}{\pi} \lim_{\epsilon \rightarrow 0} \left\{ \int_{-\infty}^{t-\epsilon} \frac{x(\tau)}{t-\tau} d\tau + \int_{t+\epsilon}^{+\infty} \frac{x(\tau)}{t-\tau} d\tau \right\}$, where $x(t)$ is the original signal (Bendat and Piersol, 1986). The Gabor analytic signal $Z(t)$ is defined as $Z(t) = x(t) + ih(t) = a(t)e^{i\varphi(t)}$, and the phase of the signal was obtained as $\varphi(t) = \tan^{-1} \frac{h(t)}{x(t)}$ (using a four-quadrant inverse tangent). A schematic of such an analysis for 3 channels of data is shown in Fig. 1. For each time t_i in the data, the sum of the cosine, $\sum_{j=1}^n \cos(\varphi_j(t_i))$, and sine, $\sum_{j=1}^n \sin(\varphi_j(t_i))$, of the phases over all n electrodes was taken, and the average phase amplitude $r(t_i)$ and average angle $\theta(t_i)$ were calculated as

$$r(t_i) = \frac{1}{n} \sqrt{\left(\sum_{j=1}^n \cos(\varphi_j(t_i)) \right)^2 + \left(\sum_{j=1}^n \sin(\varphi_j(t_i)) \right)^2}$$

$$\theta(t_i) = \tan^{-1} \left[\left(\sum_{j=1}^n \cos(\varphi_j(t_i)) \right) + i \left(\sum_{j=1}^n \sin(\varphi_j(t_i)) \right) \right]$$

as illustrated in Fig. 1. The variable $r(t_i)$ is also known as mean phase coherence (Mormann et al., 2000), and is equivalent to (1 minus the) circular variance (Fisher, 1993). The sequential average angle $\theta(t_i)$ was unwrapped by adding 2π whenever $\text{mod}[\theta(t_i)] = 0$. The average phase amplitude within each 1 s window k , $r_k = \frac{1}{200} \sum_{i=1}^{200} r_i$, was calculated in aggregate from all electrodes. The differences of the average r and θ , $\Delta r_i = (r(t_{i+1})) - r(t_i)$ and $\Delta \theta_i = \theta(t_{i+1}) - \theta(t_i)$, were calculated within each 1 s window (199 differences from 200 points). The phase amplitude and angle dispersions are the variance of the differences, $\text{var}[\Delta r]$ and $\text{var}[\Delta \theta]$, within each window. Changes in phase amplitude dispersion have been noted to appear to change during peri-ictal recordings (Mormann et al., 2000). As signals become more coherent in phase, both phase amplitude and angle dispersion should decrease.

Discrimination numerical analysis

Discrimination was performed on the sequence of the above measurements, assembled into a matrix \mathbf{Y} where the rows are in units

of time (1 s intervals) and the columns represent the 6 multivariate measurements of power, total correlation at zero lag, total correlation at arbitrary lag, phase amplitude average, and phase amplitude and angle dispersion averaged over each second. These values give us different measures of the interaction between channels, reflecting linear, non-linear, and time lagged interactions due to propagation delays. Since with the approach that follows, adding additional measures should improve rather than impair our ability to discriminate, we have not sought to extract which measures contribute most significantly to the discrimination strength. Instead, following discrimination, we have examined which measures best characterized the difference between the different stages of the seizures.

Since we do not know the best way of partitioning each seizure into a beginning, middle, and end, we examined all possible combinations by letting the beginning period range from the first 2 s of the seizure up to the first half of the entire seizure duration, while letting the termination period range from the entire second half of the seizure to the final 2 s. Two seconds was imposed as the minimum duration of a partition, and was the minimum discretization for adjusting partitions. Such an extensive ‘brute force’ sweep of partitions would permit us to find the optimal partitioning—the one which most separated the seizure dynamically into beginning, middle, and end.

For each partitioning, we separated the data matrix \mathbf{Y} into corresponding upper, middle, and lower matrices \mathbf{Y}_1 , \mathbf{Y}_2 , and \mathbf{Y}_3 . The multivariate means of these matrices were computed as $\bar{\mathbf{y}}_j = \frac{1}{N_j} \sum_{i=1}^{N_j} \mathbf{y}_{ji}$, where \mathbf{y}_{ji} are i rows (seconds) from the matrix \mathbf{Y}_j for groups $j = 1, 2, 3$. The corresponding covariance matrices are $\Psi_i = \frac{1}{N_j} \sum_{i=1}^{N_j} (\mathbf{y}_{ji} - \bar{\mathbf{y}}_j)^T (\mathbf{y}_{ji} - \bar{\mathbf{y}}_j)$ where T indicates transpose, and the full covariance matrix for the entire data set is $\Psi_{\text{total}} = \frac{N-1}{N^2} \sum_{i=1}^N (\mathbf{y}_i - \bar{\mathbf{y}})^T (\mathbf{y}_i - \bar{\mathbf{y}})$. Pooled covariance within groups, Ψ_{within} was calculated as

$$\Psi_{\text{within}} = \frac{1}{N_1 + N_2 + N_3} [(N_1 - 1)\Psi_1 + (N_2 - 1)\Psi_2 + (N_3 - 1)\Psi_3]$$

and the between group variance is thus

$$\Psi_{\text{between}} = \Psi_{\text{total}} - \Psi_{\text{within}}$$

Fisher (1936) recognized that for any linear combination $\mathbf{z} = \mathbf{Y}\mathbf{b}$, where \mathbf{b} is a column vector of coefficients, that the variance

$$\text{var}[\mathbf{z}] = \mathbf{b}^T \Psi_{\text{total}} \mathbf{b} = \mathbf{b}^T \Psi_{\text{within}} \mathbf{b} + \mathbf{b}^T \Psi_{\text{between}} \mathbf{b}$$

and that separate groups j implies that $\Psi_{\text{total}} \gg \Psi_{\text{within}}$.

Our goal is to find the discrimination function $Z(\gamma)$ that best emphasizes the between with respect to the within covariances, or in other words to maximize the ratio

$$\frac{\mathbf{b}^T \Psi_{\text{total}} \mathbf{b}}{\mathbf{b}^T \Psi_{\text{within}} \mathbf{b}} = 1 + \frac{\mathbf{b}^T \Psi_{\text{between}} \mathbf{b}}{\mathbf{b}^T \Psi_{\text{within}} \mathbf{b}} = 1 + \alpha$$

over all vectors of coefficients \mathbf{b} . Then $Z(\gamma) = \mathbf{Y}\mathbf{b}$ will be the optimal discriminator, and the maximum α will quantify the excess between covariance.

Fisher’s insight (Flury, 1997) was that this maximization can be achieved with a simultaneous spectral decomposition of $\frac{\mathbf{b}^T \Psi_{\text{between}} \mathbf{b}}{\mathbf{b}^T \Psi_{\text{within}} \mathbf{b}}$

$$\max \left[\frac{\mathbf{b}^T \Psi_{\text{between}} \mathbf{b}}{\mathbf{b}^T \Psi_{\text{within}} \mathbf{b}} \right] \Rightarrow \frac{\mathbf{b}^T \mathbf{H} \mathbf{H}^T \mathbf{b}}{\mathbf{b}^T \mathbf{H} \mathbf{H}^T \mathbf{b}} = \frac{\mathbf{b}^T \mathbf{\Lambda} \mathbf{b}}{\mathbf{b}^T \mathbf{b}} = \alpha$$

Maximizing α leads to $k = 1, \dots, m$ orthogonal linear combinations $\mathbf{z}_k = \mathbf{Y}\gamma_k$, where γ_k are the columns of $(\mathbf{H}^T)^{-1} \mathbf{\Lambda}$ is a diagonal matrix, whose values $\lambda_1 \geq \dots \geq \lambda_m > 0 = \lambda_{m+1} = \dots = \lambda_p$, where p are the number of variables, in our case 6. Thus,

there are m canonical discrimination functions, \mathbf{z}_k , which are linear combinations $\mathbf{Y}\gamma_k$ corresponding to the non-zero eigenvalues $\lambda_{1,\dots,m}$.

In computing this spectral decomposition, we have found that instabilities arise from eigenvalue calculations involving plug in estimates of Ψ_{within} and Ψ_{between} using dynamical measures of EEG. This is a general problem for the application of Fisher's method to any multivariate data, and is an impediment to the application of this technique to neuronal data such as ours.

We will focus on a singular value decomposition (SVD) based approach to finding the optimal discrimination functions. SVD is a favorable strategy for efficient matrix computations due to its favorable error handling properties. For example, least squares calculations are often solved by the normal equations in theory, but an approach using the SVD is the preferred choice if the calculation is data intensive, and especially if noisy or uncertain data are involved. In essence, the SVD determines a convenient orthogonal change of basis with which to apply matrix computations. The condition number (ratio of largest to smallest singular values) of such matrices determines the sensitivity of such solutions to errors and noise in the data. The favorable rotation of coordinates and orthogonality of SVD causes inadvertent large projections of small errors to be avoided, and helps preserve good "conditioning" of multilinear problems. In addition to providing additional stability of solutions compared with alternative approaches to discriminant solutions (Flury, 1997), our use of SVD will have the benefit of a transparent geometry with which to interpret the analysis.

The right change of coordinates simplifies the discrimination problem considerably. Let $\Psi_{\text{within}} = \mathbf{U}\mathbf{S}\mathbf{U}^T$ be the singular value decomposition (SVD) of Ψ_{within} , where \mathbf{S} is diagonal, and \mathbf{U} appears twice because covariance matrices are symmetrical. Define a new variable $\mathbf{v} = \mathbf{U}\mathbf{S}^{1/2}\mathbf{U}^T\mathbf{b}$, or equivalently $\mathbf{b} = \mathbf{U}\mathbf{S}^{-1/2}\mathbf{U}^T\mathbf{v}$. In terms of \mathbf{v} ,

$$\alpha = \frac{\mathbf{v}^T \mathbf{U}\mathbf{S}^{-1/2}\mathbf{U}^T \Psi_{\text{between}} \mathbf{U}\mathbf{S}^{-1/2}\mathbf{U}^T \mathbf{v}}{\mathbf{v}^T \mathbf{U}\mathbf{S}^{-1/2}\mathbf{U}^T \Psi_{\text{within}} \mathbf{U}\mathbf{S}^{-1/2}\mathbf{U}^T \mathbf{v}}$$

$$= \frac{\mathbf{v}^T \mathbf{U}\mathbf{S}^{-1/2}\mathbf{U}^T \Psi_{\text{between}} \mathbf{U}\mathbf{S}^{-1/2}\mathbf{U}^T \mathbf{v}}{\mathbf{v}^T \mathbf{v}}$$

This is a much better coordinate system in which to do the maximization. Since the length of \mathbf{v} scales out of the ratio, it is equivalent to maximize over unit vectors \mathbf{v} . We know that, in general, the maximum of $\mathbf{v}^T \mathbf{A}\mathbf{v}$ for a symmetric matrix \mathbf{A} is reached for $\mathbf{v} = \mathbf{v}_1$, the first singular vector of \mathbf{A} . Furthermore, the maximum subject to being orthogonal to \mathbf{v}_1 is \mathbf{v}_2 , the second singular vector of \mathbf{A} , etc. So the maximization is solved by taking the SVD

$$\mathbf{U}\mathbf{S}^{-1/2}\mathbf{U}^T \Psi_{\text{between}} \mathbf{U}\mathbf{S}^{-1/2}\mathbf{U}^T = \mathbf{V}\mathbf{A}\mathbf{V}^T$$

and the maximum α is $\mathbf{v}_1^T \mathbf{V}\mathbf{A}\mathbf{V}^T \mathbf{v}_1 = \lambda_1$, the largest singular value from \mathbf{A} . Converting back to \mathbf{b} -coordinates, the optimal \mathbf{b} , called the *first canonical variate*, is

$$\mathbf{b}_1 = \mathbf{U}\mathbf{S}^{-1/2}\mathbf{U}^T \mathbf{v}_1$$

which is the first column of $\mathbf{U}\mathbf{S}^{-1/2}\mathbf{U}^T \mathbf{V}$. The second column \mathbf{b}_2 of $\mathbf{U}\mathbf{S}^{-1/2}\mathbf{U}^T \mathbf{V}$ is the second canonical variate, and so on. The m canonical variates $\mathbf{b}_1, \dots, \mathbf{b}_m$, are the m columns of $\mathbf{U}\mathbf{S}^{-1/2}\mathbf{U}^T \mathbf{V}$. They provide the coefficients of m canonical discrimination functions $\mathbf{Z}_i(\gamma) = \mathbf{Y}\mathbf{b}_i^T$.

Clearly the choice $\mathbf{b} = \mathbf{U}\mathbf{S}^{-1/2}\mathbf{U}^T \mathbf{v}$ was a good one, but what is the intuition behind it? The geometry is shown in Fig. 2A. The

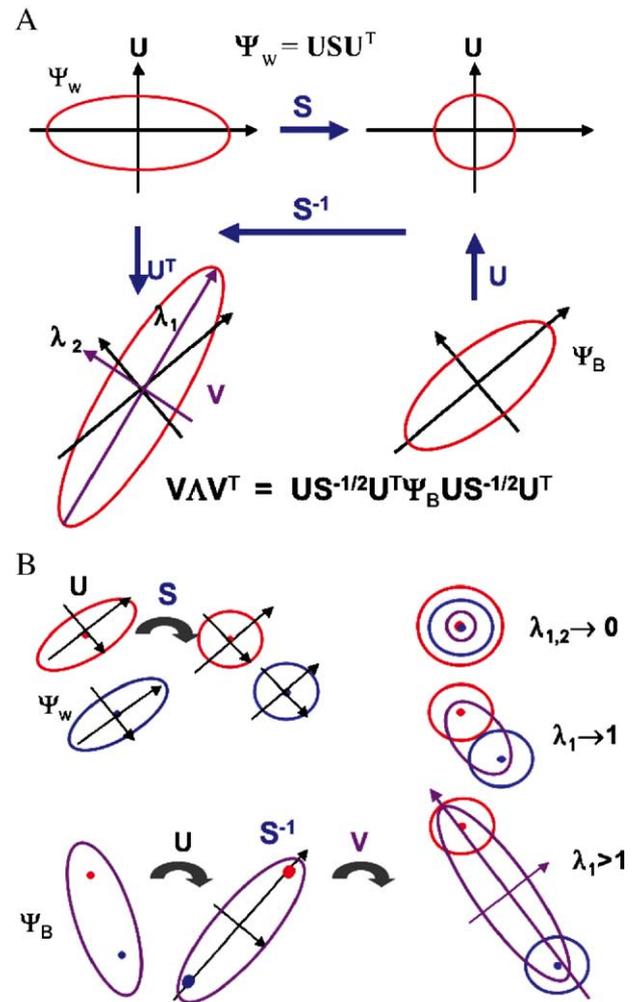


Fig. 2. Geometry of Fisher canonical discrimination with new approach to numerical analysis. In panel A, we show schematically the cloud of data points from which the within group covariance is derived, Ψ_{within} . These data are transformed with transformation \mathbf{S} to the unit circle in coordinates \mathbf{U} . Similarly, the cloud of mean points from which the covariance Ψ_{between} is derived is transformed into the \mathbf{U} coordinate system. An inverse transformation, \mathbf{S}^{-1} is applied to the mean points, so that, for instance, compression (expansion) of within group values along a certain axis is now applied as expansion (compression) to separate (bring closer) the means. The mean values are now brought out of the \mathbf{U} coordinate system through \mathbf{U}^T , and the major and minor axes of the ellipse characterized by λ_1 and λ_2 . We see in panel B how this applies to 2 data sets with 2 means. Each data set (one red, the other blue) is transformed so that their within group covariances, Ψ_{within} , are unity. Their means (red and blue dots below) are brought into the \mathbf{U} coordinate system, inverse transformed with \mathbf{S}^{-1} , and brought back to their original coordinates. The 3 general cases are shown on the right side. If the unit covariances and means overlap, then $\lambda_{1,2}$ are near zero, indicating that the means, and hence the groups, are not discriminable. The second case shows where the means are separated by a largest λ_1 which approaches unity. This case is barely discriminable. Finally, in the lower case, we see that the means are separated by a largest λ_1 which is greater than unity. In this latter case, after adjusting the within group covariances to unity, the means remain separable by a large enough distance so that they are likely to have been selected from groups with different means. This is the fundamental feature of discriminable groups.

transformation simply scales linearly along the principal axes of the within covariance ellipsoid, so as to make the within ellipsoid the unit sphere. The magnitude of the principal axes of the resulting between ellipsoid are the optimal λ_i .

To see this, note that the coordinate change consists of three transformations. First, use \mathbf{U}^T to change to the coordinate system where the covariance matrix Ψ_{within} is a diagonal matrix (where the corresponding Ψ_{between} covariance ellipsoid is aligned with the coordinate axes). Second, shrink the i th coordinate axis by a factor of $(\sqrt{s_i})^2 = s_i$. Third, change back to the original coordinate system. After these three transformations, the Ψ_{within} covariance ellipsoid was squeezed to the unit ball, normalizing the within covariance to better evaluate the size of the Ψ_{between} covariance ellipsoid. The magnitude of the principal axes of the resulting Ψ_{between} covariance ellipsoid are now the λ_i , and the semi-major axes are in the direction of the \mathbf{b}_i .

Fig. 2B illustrates the 3 general cases from this geometrical transformation. All within group covariances are transformed into unit spheres. The means of each group are stretched or shrunk by an amount that is the inverse of the transform required to create the unit spheres. On the right hand side, the first case is that the eigenvalues λ_i approach zero. There is no discrimination possible because the means and covariances of the groups overlap nearly completely. The second case is where the eigenvalue λ_1 approaches 1. Here, the unit spheres are just touching, which is the threshold for discriminating 2 groups. In the final case, $\lambda_1 > 1$, and the means of the two groups are separated by more than the within group covariances, implying that these data are discriminable into two separate groups.

Testing discrimination quality

For each multivariate data vector \mathbf{Y} (sample of power, average phase amplitude, 2 correlation measures, and 2 phase dispersions), the transformed vectors \mathbf{z} have means \mathbf{u} and normal p -variate distributions $f(\mathbf{z})$. Prior probabilities π_j are determined from the fraction of total samples within group j , $\pi_j = N_j / N$. The posterior probability π_{jz} is the probability that for a given value of \mathbf{z} , that the data came from group j of n groups

$$\pi_{jz} = \frac{\pi_j f_j(\mathbf{z})}{\sum_{k=1}^n \pi_k f_k(\mathbf{z})}, k = 1, \dots, n$$

A suitable approximation to $\pi_j f_j(\mathbf{z})$ is given by $\exp[q(\mathbf{z})]$ where $q(\mathbf{z}) = \mathbf{u}_j^T \mathbf{z} - \frac{1}{2} \mathbf{u}_j^T \mathbf{u}_j + \ln \pi_j$ (Flury, 1997). The highest posterior probability among all possible groups is the predicted group membership used in our calculations.

A robust method of testing the quality of classification is to leave one multivariate data point out of the calculation of the discriminant function, and then test for predicted group classification given its posterior probability.

A normal theory method to test for the significance of discrimination is to examine the magnitude of the eigenvalues of Λ above. We make use of Wilks' statistic, W . After calculating the log likelihood ratio as $\text{LLRS} = N \sum_{i=1}^m \ln(1 + \lambda_i)$, where λ_i are the diagonal entries of Λ , $W = \exp[-\frac{1}{N} \text{LLRS}]$. A poor discrimination yields small eigenvalues λ_i , and W approaches 1. Good discrimination yields large eigenvalues, and W becomes small. Since W is chi-squared distributed, we can calculate confidence limits that the discrimination is significant (Flury, 1997).

We have compared our new numerical approach with more standard numerical analysis (Flury, 1997) for the original Fisher data set of morphometric measurements from 3 different iris flower species. The canonical discrimination functions are, up to an arbitrary sign, identical, and the W calculated by both methods is identical (and highly significant).

Since we derive W from assumptions of normal distribution of data variables with equal covariances, which our real data will deviate from, an alternative means of testing the quality of discrimination is to randomly permute the labeling of each multivariate data point (to beginning, middle, or end of seizure groups), and re-test the goodness of fit. Although there are theoretically $N!/N_1 N_2 N_3$ possible combinations for each of the three groups (where N is the total number of measurements, and N_i are the number within each partition), we will limit our permutations to 1000.

In summary, we will present three different measures of the substantiality of discrimination: leave one out error rate, W and its normal theory confidence limits, and a bootstrapped confidence limit that is robust against deviations from normality in the data structure.

A full copy of working source code (written in Matlab) along with a data sample (Scalp subject B, from Fig. 4) is archived as Supplementary data).

Models of coupled systems

In order to help interpret our findings, we will also build sequentially more complex linear autoregressive (AR) models of coupled systems. These systems and resulting analysis are illustrated in Fig. 3. We started with a 4 channel AR system, and by brute force progressively increased the complexity in order to create the simplest linear systems capable of replicating our findings. The simplest AR model is

$$x_1(t) = ax_1(t-1) + \xi_1(t)$$

$$x_2(t) = ax_2(t-1) + \xi_2(t)$$

$$x_3(t) = ax_3(t-1) + \xi_3(t)$$

$$x_4(t) = ax_4(t-1) + \xi_4(t)$$

where for 4 channels of simulated data, $x(t)_1 \dots x(t)_4$, each value at time t is coupled to the previous value within the channel at time $t-1$, with the addition of an independent Gaussian distributed random value $\xi(t)$. The model is seeded with random initial conditions. This model generates a data set without coupling between the 4 channels.

Our next AR model of interest will be

$$x_1(t) = ax_1(t-1) + bx_2(t-1) + \xi_1(t)$$

$$x_2(t) = ax_2(t-1) + \xi_2(t)$$

$$x_3(t) = ax_3(t-1) + bx_4(t-1) + \xi_3(t)$$

$$x_4(t) = ax_4(t-1) + \xi_4(t)$$

where the first channel is coupled to the second, and the third channel is coupled to the fourth, but there is no coupling between channels 1 and 2 with channels 3 and 4.

The final AR model is more complex

$$x_1(t) = ax_1(t-2) + bx_2(t-2) + cx_2(t-4) + dx_2(t-6) + \xi_1(t)$$

$$x_2(t) = ax_2(t-2) + \xi_2(t)$$

$$x_3(t) = ax_3(t-2) + bx_4(t-2) + cx_4(t-4) + dx_4(t-6) + \xi_3(t)$$

$$x_4(t) = ax_4(t-2) + \xi_4(t)$$

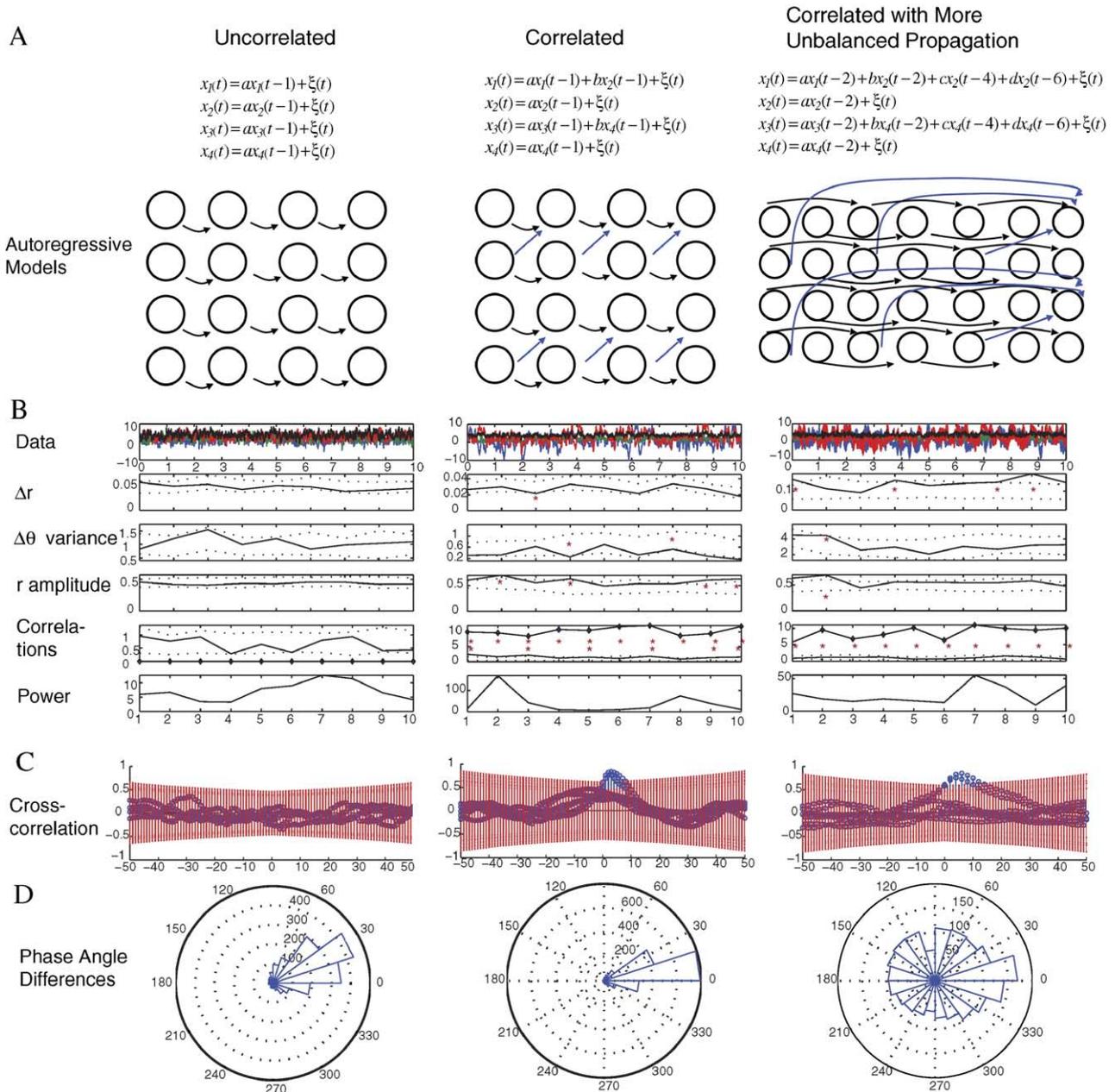
Here, there are significant propagation delays in the coupling both within each channel, and between channels. Again, only channels 1 and 2 and channels 3 and 4 are coupled to each other.

Results

Our discrimination analysis (see Methods) functions geometrically by renormalizing the covariances of each group’s within group covariance, and disentangling the overlap between group mixtures so that the separation of group means is maximal (Fig. 2).

Twenty-four seizures (12 scalp, 12 intracranial) were studied for the presence of significantly discriminable beginnings, middles, and ends.

Twelve scalp seizures were selected for detailed analysis, from 79 consecutive scalp seizure records (excluding those with only absence or myoclonic seizures), because they were sufficiently free of artifact (determined by two investigators) to permit detailed dynamical study. The remaining scalp recordings utilized standard 10–20 electrode placement obtained from 5 children (labeled



subjects A through E) 2.3 to 12 years of age. One child had cryptogenic generalized seizures not being treated at the time of the recording and the others were receiving 2–3 anticonvulsants. The symptomatic seizures were a consequence of bi-occipital gliosis, cerebellar atrophy with history of prior hemiparesis, bi-parietal encephalomalacia and ventriculomegaly, and cortical laminar disorganization with dysgenic hippocampus. Each child had 1–5 partial seizures with or without secondary generalization analyzed. The montage and an example from one subject (scalp subject B) are shown in Figs. 4A and B.

Twelve intracranial seizure records from 4 patients (labeled A through D) with disparate seizure types and etiologies were without significant electrical artifact (from 16 consecutive records) and were selected for further study. Subject A had a dysplastic posterior temporo-parietal cortex, subject B had frontal gliosis, subject C had a small cortical low grade astrocytoma with highly focal seizures confined to a several square centimeter region near the tumor, and subject D had both a dysplastic occipital lobe and mesial temporal sclerosis (Fig. 5A). An example of a seizure from subject D is shown in Fig. 5B. Of 16 consecutive intracranial seizures for these patients, 12 were selected as free from artifact after no more than 1 bad channel was eliminated from analysis. In all, 3 seizures were selected for each of the 4 intracranial subjects.

Examples of the dynamical data calculations without regard to discrimination are shown in Figs. 4E and 5E. We examined all possible partitions of such data to divide the seizure into beginning, middle, and terminal segments. This is done by letting the beginning period vary from 2 s to up to half of the seizure in length, and similarly letting the terminal period vary from the last 2 s to the last half of the seizure in length. All possible combinations (in units of 2 seconds) of partitioning into beginning, middle, and end are then tested for quality of discrimination using Wilks' statistic, W (see Methods, note that optimizing on error rates would have been an alternative), and the optimal partition combination chosen.

An example of the result of such partition optimization for a scalp seizure is shown in Fig. 4C. The minimal value of W was 0.12, which is much less than the value of 0.75 expected by the chi-squared distribution for W ($df = 12$, $p = 0.01$, see Fig. 4D). Since W assumes normally distributed variables, we checked the integrity of our discrimination by randomly reassigning the original measurements (6 measures combined) to different assignments within this optimal partition (beginning, middle, and end), and then repeated the calculation of W . For 1000 iterations of this reassignment, this bootstrap shows that the partition is highly unlikely to have been seen by chance, with a probability of less than 0.001 (Fig. 4F). The plot of the first and second discriminants (linear combinations of original variables) of this optimal partition, z_1 and z_2 , are shown in Fig. 4D. We find that the leave one out error rate for this optimal discrimination is 11%.

Note the seizure partitions expanded in more detail at the top of Fig. 4E. The optimization segmented the seizure into 3 stages that contain, respectively, a rhythmic partial onset, tonic middle, and clonic terminal activity to visual inspection.

Discrimination into 3 groups was possible for all 12 scalp seizures, with significance by W ($p < 0.01$) and bootstrap ($p < 0.001$) for all seizures.

Similar analysis for an intracranial seizure from subject D is shown in Fig. 5. The minimal value of optimized W was 0.16 (Fig. 5C), which is much less than the value of 0.88 expected by the chi-squared distribution for W ($df = 12$, $p = 0.01$), and a plot of the first and second discriminants is shown in Fig. 5D. One thousand bootstrap permutations show that this partitioning is highly unlikely to have been seen by chance, with a probability of less than 0.001 (Fig. 5F). We find that the leave one out error rate for this optimal discrimination is 16%.

Note the seizure partitions expanded in more detail at the top of Fig. 5E. The optimization segmented the seizure into 3 stages that contain substantially different patterns evident by visual inspection.

Fig. 3. Autoregressive simulations and data analysis. Three progressively more complex autoregressive models, and their data analysis, are illustrated. In the uncorrelated model (first column, panel A), each of the 4 simulated channels is equal to a constant, $a < 1$, multiplied by the previous data value ($x_i(t-1)$), plus a random shock $\zeta(t)$, which is independently applied to each channel 1–4 at each time t . The channels are uncoupled to each other. In B, the Δr variance shows that the phase dispersion of these channels within each 200 point data window lies within the 98% confidence limits (dotted lines) set by recalculating Δr variance from 100 sets of surrogates for each data window as outlined in the legend from Fig. 1. Similarly, $\Delta\theta$ variance is within that expected for uncoupled systems. The average r amplitude shows no evidence of coupling, and both the zero lag (solid line, compared with surrogates, dotted line) and the arbitrary (all) lag correlation sums (diamonds, compared with the Bartlett, 1946 estimator as detailed in Methods) show no evidence of correlation. In panel C, examples of several pairs of crosscorrelation plots for different channels within the first data window are shown, and the red error bars show twice the standard deviation (\pm two times the absolute value of the Bartlett estimator of standard error). No values of crosscorrelation exceed the confidence limits. Lastly, plots of the distribution of phase angle differences within a data window are plotted on the circle. Note that, in this uncoupled case, the similar spectral frequency (a is constant) within each channel produces a distribution of phase angle changes which are clustered about a well defined mean change. All of this is the picture of a set of uncoupled processes which have well defined autocorrelation. In the middle column, the correlated model, we couple channels 1 to 2, and 3 to 4, with short propagation delays. Note in the data analysis in panel B that both Δr and $\Delta\theta$ variances now have some values which are smaller than expected from the surrogate data, which reflects the coupling present. The average r amplitude is now consistently higher than expected for an uncoupled system, and both zero (solid line) and non-zero (diamonds) lagged crosscorrelations are higher than expected for uncoupled systems. Note that, in the plots of crosscorrelation in panel C, some channel pairs are not correlated—channels 1 to 3 or 1 to 4 for instance. Other channel pairs which are correlated reveal a peak in crosscorrelation which is higher than expected by the Bartlett estimator, and although they show a time lag reflecting the lag in coupling, the values at zero lag remain significant. Note that the distribution of angle differences in panel D is now more tightly clustered, reflecting the coupling. In the right column, we show a more complex correlated model with more unbalanced propagation delays. Here, we have introduced propagation delays both within and between channels, and used propagation delays greater than 1 time step (2 to 6 time steps). Again, the system is compartmentalized in order to unbalance the system into channels 1 to 2 and 3 to 4, which only communicate within each pair. Now in panel B, we see that the Δr variance is higher than expected. Note in panel D that the $\Delta\theta$ angle differences are now scattered uniformly over the unit circle. The $\Delta\theta$ variance is no longer decreased as in the middle column, and the r amplitude is less elevated. The zero lag crosscorrelation no longer reflects a coupled system (values at 0 lag are no longer above the confidence limit). However, the arbitrary lag sum of crosscorrelation values (diamonds) easily pick up that this system has significant crosscorrelation. We built up these autoregressive systems by brute force, searching for the simplest linear model which would reflect our experimental findings. This latter case, with prominently increased Δr variance in the setting of increased non-zero lagged crosscorrelation, simulates our main findings well.

Discrimination into 3 groups was significant by W ($p < 0.01$) for 12 of 12 seizures, but confirmed by bootstrap for 9 of 12 ($p < 0.002$). No more than 1 seizure per patient failed to be confirmed by bootstrap.

We then normalized and averaged the results across all partitions from all subjects: pre-seizure, beginning, middle, end, and post-seizure periods. The grand average results for Scalp seizures are shown in Fig. 6. Analysis of variance (ANOVA) demonstrated that the phase dispersion ($df = 59$, $F = 8.49$, $p < 0.00001$) was significantly elevated during the middle phase of the seizures. Tukey's multiple comparison testing (Hogg and Ledolter, 1992) revealed that this increase in phase dispersion was significant in comparison with both pre- and post-seizure periods. Since seizures were unevenly divided among 5 subjects (1, 1, 1, 3, and 6 seizures, respectively), we checked all possible combinations of choosing 1 seizure from each subject, and recalculated the grand averages: all 18 combinations of 5 seizures revealed significant ($p < 0.05$) increases in phase dispersion during the middle phase of seizures. Correlation sums at arbitrary lag were similarly significantly elevated during the middle phase of seizures ($df = 59$, $F = 11.52$, $p < 0.000001$). Again, checking all possible combinations of choosing 1 seizure from each subject, and recalculating the grand averages, all 18 combinations of 5 seizures revealed significant ($p < 0.05$) increases in correlations during the middle phase of seizures.

We next examined intracranial grand averages (Fig. 6). Phase dispersion ($df = 59$, $F = 3.4$, $p < 0.02$) revealed elevated values during the beginning of seizures, and multiple comparison testing (Tukey test) revealed that this elevation was predominantly in relation to post-seizure dispersions. Similar to the scalp seizures, correlation sums at arbitrary lag were similarly significantly elevated during the middle phase of seizures ($df = 59$, $F = 4.9$, $p < 0.002$). Again, checking all possible combinations of choosing 1 seizure from each subject and recalculating the grand averages, all 81 combinations of 4 seizures revealed significant ($p < 0.05$) increases in correlations during the middle phase of seizures.

The issue of propagation critically affects the observation of correlation in these data. If only the correlations at zero lag were considered, one would have identified significant amplitude correlations in only 3 scalp (2 subjects) and 4 intracranial (3 subjects) seizures, and the aggregate would not have revealed significant correlations.

The most common pattern of dynamics which underlay our findings was the simultaneous increase in synchronization (cross-

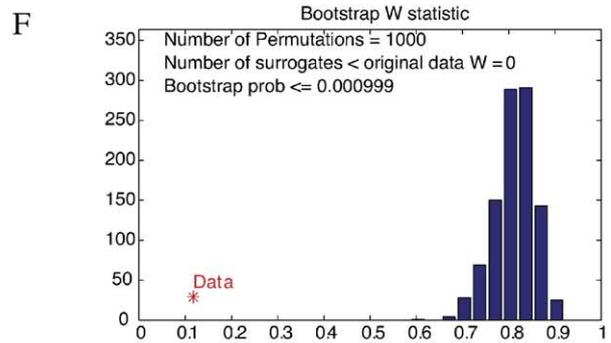
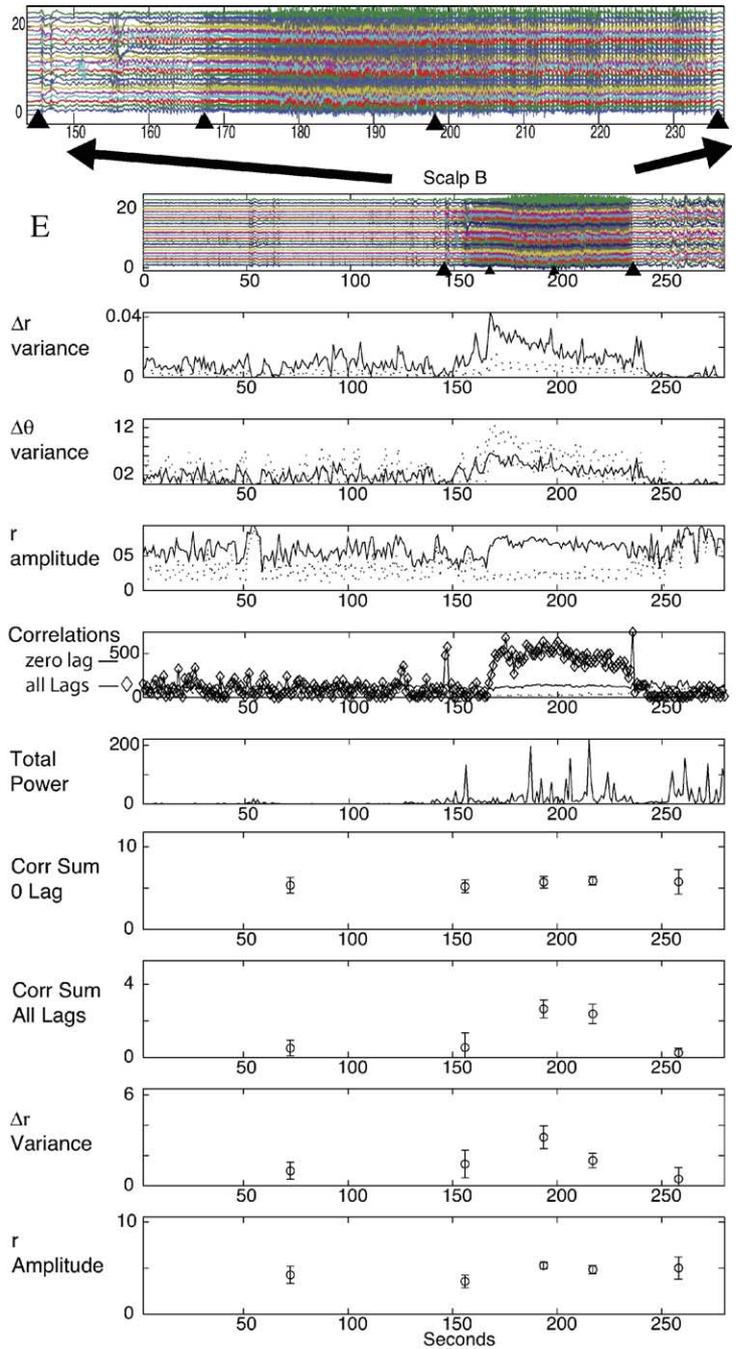
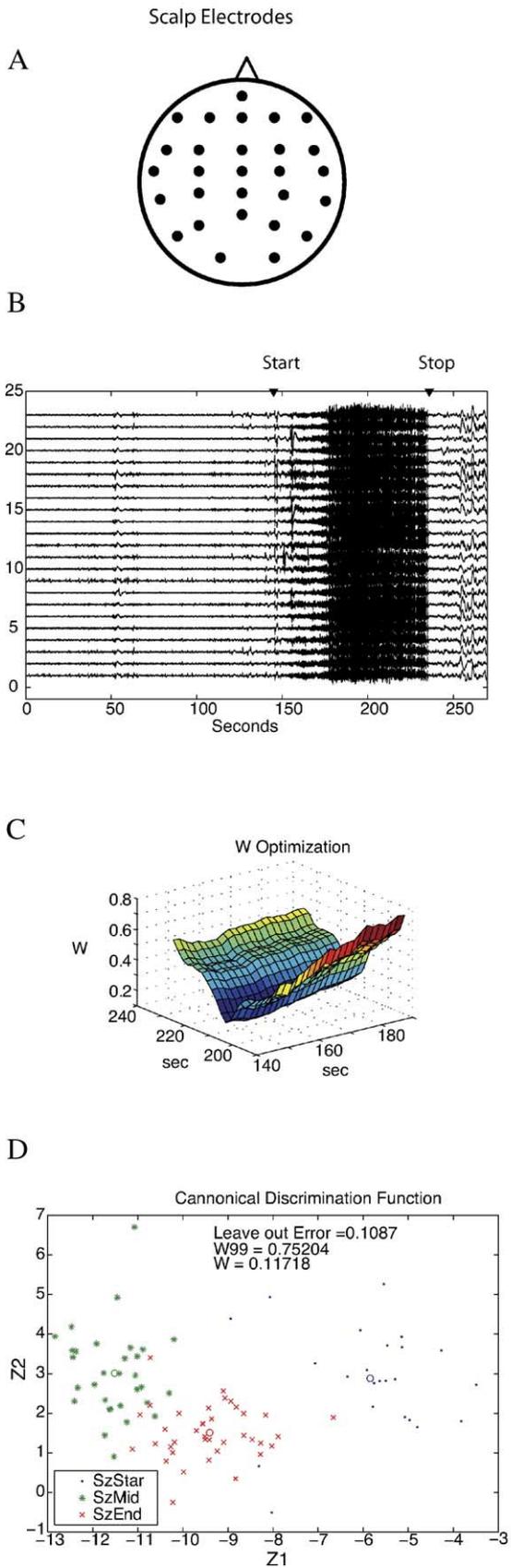
correlation sum at arbitrary lag) during the middle phase of seizures, accompanied by an increase in phase dispersion. How can we attempt to account for what appears at first to be a rather counterintuitive set of findings—the increasing phase dispersion would be expected to characterize asynchronous coupled systems? To provide a possible explanation, we have constructed a series of progressively more complex linear autoregressive model systems. In Fig. 3A, we show a simulated 4 channel system where each channel is made up of independent systems whose values depend on the most recent previous values. Such a system appears uncorrelated in all measures of amplitude or phase applied (Fig. 3B), but note that the phase angle differences are rather narrowly confined (Fig. 3D). Given more time, such a system would demonstrate increasing phase dispersion, but for such finite data sets with similar native frequencies, one would be misled without appropriate bootstrap statistics as used here (Fig. 3B). In the second column, we show data from coupling channels 1 to 2, and channels 3 to 4, with the shortest possible propagation delays. Phase coherence (r amplitude) now shows significant coupling, as does both zero and arbitrary lagged correlation sums. Note that the phase angle dispersion is decreased in Figs. 3B and D. Lastly, note the more unbalanced state in column 3 with substantial propagation delays in coupling. Now, although the arbitrary lag correlations are significant, the zero lag correlations are not. Note that in the correlation plots (Fig. 3C), one can see that the propagation delays prevent the zero lagged correlations from being significant, while longer lag correlations are significant. Most importantly, note that the phase angle dispersions are now dramatically and highly significantly increased (Figs. 3B and D).

We built up these autoregressive systems by brute force, searching for the simplest (4 channel) linear model that would reflect our experimental findings. The final pattern, seen by progressively unbalancing an autoregressive system and introducing significant propagation delays, mimics the actual EEG results closely.

Discussion

We have constructed a novel interpretation of the geometry of R.A. Fisher's 1936 method of canonical multivariate discrimination analysis. A remarkable intellectual feat in the 1930s, Fisher never wrote down a geometrical interpretation of his analysis. Instead, the original report was more of a recipe for others to apply

Fig. 4. Scalp electrode analysis. In panel A are shown the electrode positions for the 10–20 electrode montage, and in panel B is illustrated a complete 23 electrode tracing of a scalp seizure from subject B contained within a 5 min recording. Note that the start and stop times are chosen by visual inspection. Panel C illustrates the optimization of Wilks' Lambda for all possible partitions (seconds) of the seizure time into beginning, middle, and end. Panel D illustrates a plot of the first 2 canonical linear discriminants, z_1 and z_2 , color coding the beginning (SzStart), middle (SzMid), and end (SzEnd) of the seizure into blue dots, green asterisks, and red \times marks. The means of these transformed groups are shown as colored open circles. The variances about these means clearly shows that these groups are discriminable by visual inspection, and shown are the relevant leave one out error rates, 99% confidence limit for W by Chi-squared analysis, and the low value of W , all consistent with a highly discriminable optimal partitioning of this seizure. In panel E is shown the time course of all data that went into this analysis, along with relevant confidence limits. The top plot shows each raw data channel, color coded to bring out contrast in changing patterns (alternate channels have different colors), and the optimal partition indicated by inverted triangles (\blacktriangle) into beginning, middle, and end periods. The seizure partitions are further expanded to show detail above. Note that the Δr variance increases during the seizure buildup, and is prominently elevated above the 99% confidence intervals based on surrogate data (2 dotted lines). Note that the $\Delta\theta$ variance does not show changes outside of the confidence limits. The r amplitude increases most prominently during the middle and end of the seizure, as do arbitrary (all) lagged correlations. At the bottom are shown the means and standard deviations of the 2 correlation measures, Δr variance, and r amplitude. Note that there are no significant changes in mean for the zero lagged correlation values, and the phase amplitudes. The non-zero correlation sums and Δr variance show very significant elevations during the middle phase of this seizure. In panel F are shown the bootstrap results for 1000 random permutations of the group assignments of these data (equivalent to randomly recoloring the plot in panel D), and calculating W . Note that the small significant value for our optimum partition (red asterisk) is much lower than any other permutation result, indicating that our partitioning is highly unlikely to be due to chance.



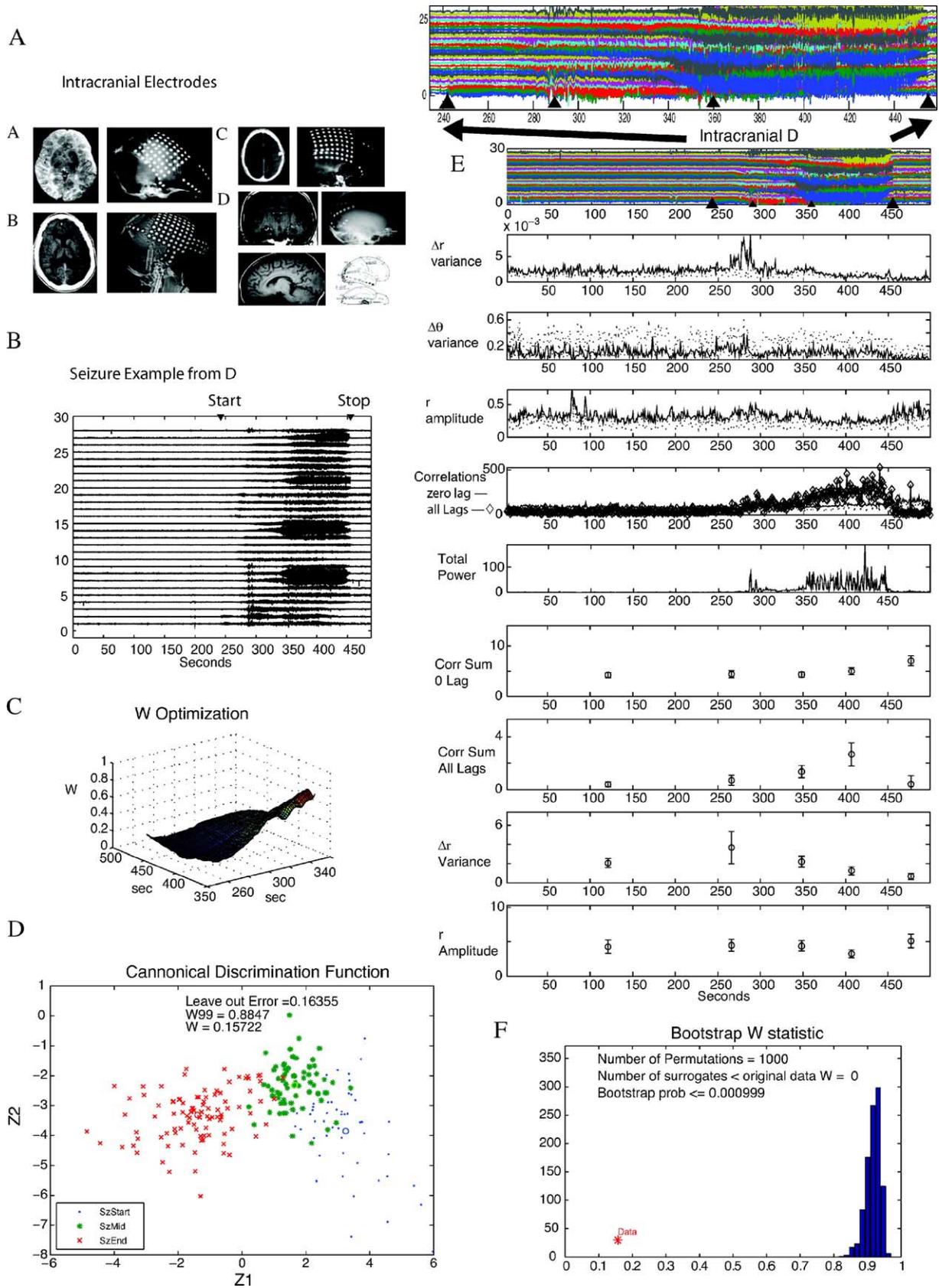


Fig. 5. Intracranial electrode analysis. Similar to Fig. 4, except that the electrode montages are now indicated for subdural, and in the case D, mixed subdural and depth electrode assemblies. Note that for intracranial data, that the increase in Δr variance is more prominent during the beginning of the seizure, while the non-zero lagged correlations are not prominent until late in the seizure.

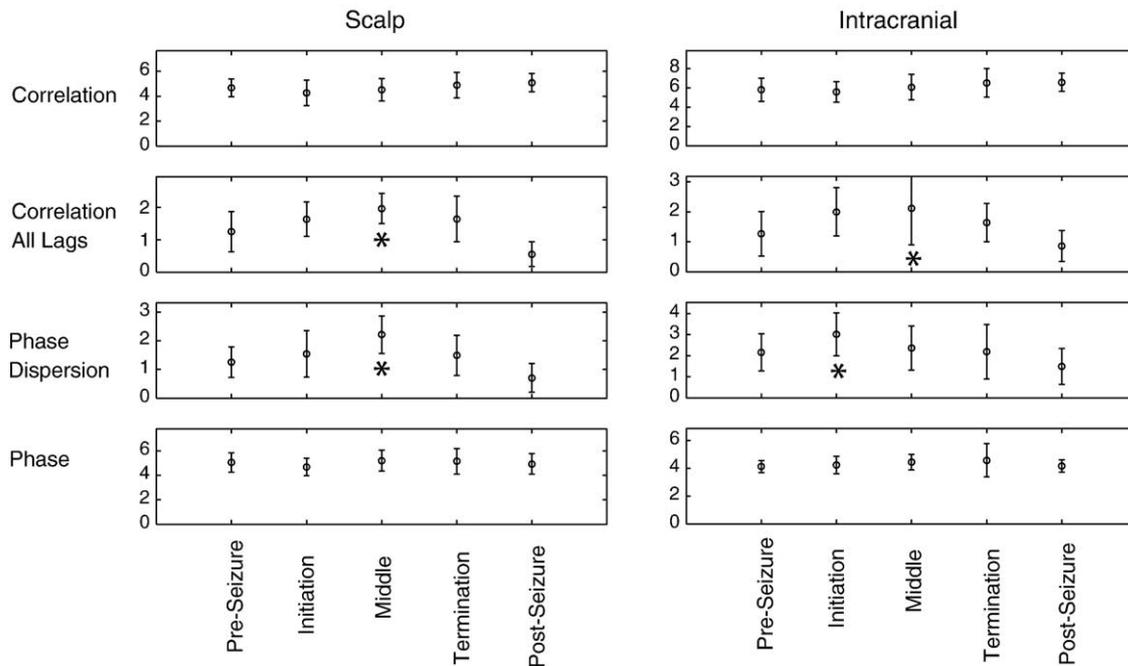


Fig. 6. Grand average results for scalp and intracranial recordings. The results of all data were normalized and averaged within groups as pre-seizure, initiation, middle, termination, and post-seizure periods. Four variables are shown to highlight the results of interest in phase dispersion and correlation. ANOVA for Scalp seizures indicated significant changes in arbitrary (all) lag correlations ($df = 59$, $F = 11.52$, $p = 7.3 \times 10^{-7}$) and Δr variance ($df = 59$, $F = 8.49$, $p = 2.1 \times 10^{-5}$), and multiple comparison Tukey tests confirmed that the peak values of non-zero lag correlations and Δr variances were significantly higher than the pre- and post-seizure values, accounting for these ANOVA results. Intracranial seizures again showed significant ANOVA differences in aggregate mean for arbitrary lag correlations ($df = 59$, $F = 4.86$, $p = 0.002$) and Δr variances ($df = 59$, $F = 3.36$, $p = 0.02$), the peak in the arbitrary lag correlations significantly higher than the post-seizure period (Tukey test), and the Δr variance was most prominently elevated during the beginning of the seizure (compared with post-seizure by Tukey test).

this technique to morphometric data. Such data did not envision the data structures created from a signal processing analysis of neuronal signals, nor the developments in applied mathematics and numerical analysis that accompanied the advent of digital computers. We have shown a stable approach with a clear geometrical interpretation to solving his original linear analysis for the examination of data such as used in this report. Our approach can be used in many other settings (EEG, MEG, Optical Imaging, fMRI), and we offer our algorithms for others to make use of in the Supplementary data.

Using this method, we report the first canonical discrimination analysis to search for dynamically distinct stages of epileptic seizures in humans. We found significant extraction of unique initial and terminal phases from 21 of 24 scalp and intracranial recordings. These results argue for an evolution of seizure patterns that can be consistently partitioned based on dynamical measures.

Nonlinear methods to compute Fisher discriminants have been developed in recent years using kernel-based approaches (Muller et al., 2001). Similarly, one might ask whether using non-linear dynamical EEG measures instead of our linear ones might have improved the results of our linear or an alternative non-linear discrimination method. Notwithstanding that we anticipate that neuronal dynamics are fundamentally non-linear, our robust results with linear methods here may reflect a more general phenomenon seen with detecting coupling in the presence of significant amounts of noise and non-linearity (Netoff et al., 2004).

There has been surprisingly little previous work quantifying the dynamical stages of seizures. In experimental kindled seizures,

Racine (1972) described progressive changes in electrical seizure patterns corresponding to behavioral manifestations. In the tetanus toxin model of experimental seizures, a staging system has been devised for different segments of seizures (Finnerty and Jefferys, 2000). For the particular case of human status epilepticus, Treiman et al. (1990) defined a staging system. In all of the above, the classification of seizure stages was based upon qualitative assessments following visual inspection of EEG. The most quantitative approaches to segmentation of seizures that we are aware of (Wendling et al., 1996; Wu and Gotman, 1998) focused upon comparing the similarities (or dissimilarities) between different seizures.

Although seizures have for over half a century been characterized as synchronous or ‘hypersynchronous’ (Penfield and Jasper, 1954), the measurements to support such conclusions have been sparse (for review see Netoff and Schiff, 2002). In our analysis, no consistent evidence of increased synchronization was evident within the initial or terminal phases of these seizures—synchronization was a prominent feature only once the seizure had passed through its initiation phase, and was a variable feature of seizure termination depending on subject. The other consistent dynamical feature of these seizures was the consistent increase in phase dispersion, which tended to be reflected during the initial stage of seizure formation intracranially, or during the middle phase of seizures recorded at the scalp. Although the scales of observation are vastly different, we note that observing intracellular currents during experimental seizures similarly shows a lack of synchronization during the initiation of such events (Netoff and Schiff, 2002).

We still lack a dynamical definition of a seizure. Although we customarily assign seizure onsets, as done in this study, by applying subjective visual inspection to EEG records, such a procedure is unsound for more definitive study of these phenomena. We require a description of the dynamics of seizure onset that is clearly discriminable from the preceding non-seizure dynamics. Our study is a first attempt to prove that the initial phase of a seizure bears unique dynamical signatures. A logical future step will be to attempt such discrimination between pre-seizure and seizure onset in an effort to objectively delineate seizure from non-seizure.

There has been intense interest in whether there exists a pre-seizure state (Ebersole, 2005, Lehnertz and Litt, 2005). Such a state, if physiologically distinct from seizure onset, would provide a means of predicting the imminent onset of a seizure. If a pre-seizure state existed for a given subject, and importantly, if the dynamics within this pre-seizure state were discriminable from seizure onset, the methodology we have described are a powerful means of delineating these states. Note that if what we think is a pre-seizure state was actually a small version of the seizure, that is a highly localized form of the seizure whose dynamics were the same as the seizure onset, then our approach would group such dynamics as part of the seizure onset.

Our findings also point to the question of how is synchrony in neural systems to be measured and observed. Although we customarily infer the presence of synchrony by observing the presence of correlations (in either signal amplitude or phase), such findings ignore the stability constraints that must be present when physical systems synchronize (Pecora and Carroll, 1998). We also customarily ignore propagation delays in synchrony measures, although such delays are inherent in all neural systems. Although we cannot use perturbations (Francis et al., 2003) to test for synchrony stability in human seizure recordings, we can compare measures of synchronization that take propagation delays into account. In our human seizure data, we found little evidence for synchronization using phase or amplitude correlations measured without permitting a time lag, but significant evidence for synchrony during the middle stages of seizures when arbitrary time lags were permitted. We also showed how an autoregressive system with significant compartmentalization and propagation delays within and between such compartments could generate evidence of increased phase dispersion in the presence of significantly increased amplitude correlations—mimicking closely the general findings of our human seizure data. Although such simulations in no way are a unique means to account for our human findings, they point to one of the simplest models capable of imitating these dynamics. Brains have compartments separated by conduction delays, and such features need to be taken into account when analyzing seizures for the presence of apparent synchronization.

Why do seizures stop? Most human subjects with epilepsy have self-limited transient seizures. Subjects with seizures that do not limit their intensity and terminate are at substantially higher risk of death. Unfortunately, we know little about the dynamical changes that terminate seizures. If seizures have a terminal phase distinct from earlier phases, then understanding how to induce such terminal dynamics may offer a unique strategy for suppressing seizures through deep brain stimulation.

Finally, how many dynamical stages constitute typical seizure evolution? Although we searched for three stages, we were most

interested in whether seizures had distinct onsets and offsets. Significant findings of discrimination into 3 separable groups is possible given more than 3 true groups, and we did not attempt to perform an optimization analysis searching for the most likely number of stages present in our evolving seizures. In addition, for a dynamical process that changes continuously (monotonically and noiselessly), the separation into a finite number of groups might be significant despite a theoretically infinite number of stages. These issues make us cautious over placing too much emphasis on a precise number of stages within these seizures. Nevertheless, despite the very different means of observation (intracranial depth and subdural versus scalp electrodes), we found consistent patterns in phase and amplitude correlation within our stages that were consistent across many subjects as seizures evolved. These findings underscore the fundamental results from applying our discrimination analysis—that seizures dynamically evolve and display distinctive initiation and termination dynamics.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at [doi:10.1016/j.neuroimage.2005.06.059](https://doi.org/10.1016/j.neuroimage.2005.06.059).

References

- Ayala, G.F., Matsumoto, H., Gummit, J., 1970. Excitability changes and inhibitory mechanisms in neocortical neurons during seizures. *J. Neurophysiol.* 33, 70–85.
- Bartlett, M.S., 1946. On the theoretical specification and sampling properties of autocorrelated time-series. *J. R. Stat. Soc. B8*, 27–41.
- Bendat, J.S., Piersol, A.G., 1986. *Random Data*. J. Wiley and Sons, New York, pp. 484–516.
- Box, G.E.P., Jenkins, G.M., 1976. *Time Series Analysis, Forecasting and Control*, (Rev edition). Holden-Day, San Francisco, FL, pp. 376–377.
- Ebersole, J.S., 2005. In search of seizure prediction, a critique. *Clin. Neurophysiol.* 116, 489–492.
- Finnerty, G.T., Jefferys, J.G.R., 2000. 9–16 Hz oscillation precedes secondary generalization of seizures in the rat tetanus toxin model of epilepsy. *J. Neurophysiol.* 83, 2217–2226.
- Fisher, R.A., 1936. The use of multiple measurements in taxonomic problems. *Ann. Eugen.* 7, 179–188.
- Fisher, N.I., 1993. *Statistical Analysis of Circular Data*. Cambridge, Cambridge, UK, pp. 30–35.
- Flury, B., 1997. *A First Course in Multivariate Statistics*. Springer, New York.
- Francis, J.T., Gluckman, B.J., Schiff, S.J., 2003. Sensitivity of neurons to weak electric fields. *J. Neurosci.* 23(23), 7255–7261.

- Hogg, V.H., Ledolter, J., 1992. *Applied Statistics for Engineers and Physical Scientists*. Macmillan, New York, pp. 271–272.
- Kandel, E.R., Spencer, W.A., 1961. Excitation and inhibition of single pyramidal cells during hippocampal seizure. *Exp. Neurol.* 4, 162–179.
- Litt, B., Esteller, R., Echauz, J., D'Alessandro, M., Shor, R., Henry, T., Pennell, P., Epstein, C., Bakay, R., Dichter, M., Vachtsevanos, G., 2001. Epileptic seizures may begin hours in advance of clinical onset: a report of five patients. *Neuron*. 30, 51–64.
- Lehnertz, K., Litt, B., 2005. The first international collaborative workshop on seizure prediction, summary and data description. *Clin. Neurophys.* 116, 493–505.
- Matsumoto, H., Marsan, C.A., 1964. Cortical cellular phenomena in experimental epilepsy, Ictal manifestations. *Exp. Neurol.* 9, 305–326.
- Mormann, F., Lehnertz, K., David, P., Elger, C.E., 2000. Mean phase coherence as a measure for phase synchronization and its application to the EEG of epilepsy patients. *Physica D* 144, 358–369.
- Muller, K.-R., Mika, S., Ratsch, G., Tsuda, K., Scholkopf, B., 2001. An introduction to kernel-based learning algorithms. *IEEE Trans. Neural Netw.* 12, 181–202.
- Netoff, T.I., Schiff, S.J., 2002. Decreased neuronal synchronization during experimental seizures. *J. Neurosci.* 22, 7297–7307.
- Netoff, T.I., Pecora, L.M., Schiff, S.J., 2004. Analytical coupling detection in the presence of noise and nonlinearity. *Phys. Rev., E* 69, 017201.
- Pecora, L.M., Carroll, T.L., 1998. Master stability functions for synchronized coupled systems. *Phys. Rev. Lett.* 80, 2109–2112.
- Penfield, W., Jasper, H., 1954. *Epilepsy and The Functional Anatomy of the Human Brain*. Little-Brown, Boston, MA.
- Racine, R.J., 1972. Modification of seizure activity by electrical stimulation: II. Motor seizure. *Electroencephalogr. Clin. Neurophysiol.* 32, 281–294.
- Treiman, D.M., Walton, N.Y., Kendrick, C., 1990. A progressive sequence of electroencephalographic changes during generalized convulsive status epilepticus. *Epilepsy Res.* 5, 49–60.
- Wendling, F., Bellanger, J.J., Badier, J.M., Coatrieux, J.L., 1996. Extraction of spatio-temporal signatures from depth EEG seizure signals based on objective matching in warped vectorial observations. *IEEE Trans. Biomed. Eng.* 43, 990–1000.
- Wendling, F., Shamsollahi, M.B., Badier, J.M., Bellanger, J.J., 1999. Time-frequency matching of warped depth-EEG seizure observations. *IEEE Trans. Biomed. Eng.* 46, 601–605.
- Wu, L., Gotman, J., 1998. Segmentation and classification of EEG during epileptic seizures. *Electroencephalogr. Clin. Neurophysiol.* 106, 344–356.