Linear and Non-Linear Measures of the Human Neonatal EEG

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Abstract

Non-linear measures (Kolmogorov entropy, correlation dimension and a surrogate based “z” score) of the underlying structure of the human neonatal EEG were made and compared to linear measures (eigenvalues) and to EEGs obtained from older children (greater than 3 years of age). Strong age dependent differences were noted for Kolmogorov entropy, the surrogate based measure of non-linearity and eigenvalues. The eigenvalues decrease with age and the Kolmogorov entropy increases with age. The measure of global non-linearity decreased with age so that it was positive in only a small fraction of the greater than 3 year old subjects.

Introduction

One of the most challenging areas of clinical EEG has been the interpretation of the EEG in human neonates. The range of the EEG waveforms and patterns considered normal is broad and the identification of abnormal waveforms quite conservative. Waveforms considered potentially epileptogenic in older infants and adults are interpreted as signs of underlying tissue abnormalities but not necessarily potentially epileptogenic (e.g. spikes or sharp waves) in neonates. The frequency spectrum of normal neonatal EEG activity encompasses frequencies considered abnormal in the older patient. The diversity of neonatal EEG waveforms has resulted in a broadening of the boundaries of what is accepted as normal, and a commensurate decline in sensitivity to pathological states. Whether alternative EEG measures, such as dynamical systems measures, might improve this circumstance is a matter of active inquiry.

Recently, there has been an acceleration of research in the area of EEG analysis, fueled by emerging technologies and methodologies. Development of the MEG, the introduction of new mathematical methods for the location of intracranial sources and the application of non-linear time series analysis to the EEG have all fueled an increase in EEG research. Of particular interest is the use of deterministic chaos to predict the time of occurrence of seizures.

Early reports of the use of deterministic chaos measures to detect seizures were quite optimistic. As more investigators became interested in the application of deterministic chaos to EEG analysis our understanding of the limitations of these metrics also increased. There followed, multiple demonstrations of circumstances in which spurious chaos values were generated, suggesting that the interpretation of these metrics should be cautious. It has now been shown, in multiple laboratories, that ictal events usually have dynamical properties unlike that seen in the interictal period. In addition, there are now several reports that deterministic chaos measures can predict seizures. These dynamical system measures seem particularly well suited as an indirect measure of the behavior of large numbers of neurons, perhaps acting as a network. The question of the relative contribution of single unit versus large networks to the unstable patterns of electrical behavior in epilepsy is a core issue in epilepsy research. Despite the high level of interest in these deterministic chaos measures we have found only one article on their developmental dependency and one article specifically directed to their application to epilepsy in children. This is a small proportion of the more than one hundred articles published in this field.

The pediatric epilepsies differ from those seen in adults in a number of ways, including the higher prevalence of a neocortical origin to the events. It is not known whether the developmental changes in the EEG signal, including its underlying structure, will have substantial impact on the utility of these measures in infants and children. Therefore, we have undertaken a program to determine whether these metrics can be reliably preformed in the pediatric aged patients, whether developmental differences preclude the application of the measurements and whether there are other age specific considerations in their clinical use.

We report on the correlation dimension, eigenvalues and Kolmogorov entropy. The correlation dimension metric was chosen since it allows us to compare our results with those obtained at other laboratories. The Kolmogorov 2 entropy was selected since preliminary studies in our laboratory have suggested that it may be particularly useful in seizure prediction, and is conceptually distinct from the correlation dimension. The eigenvalue provides a measure of the strength of linear models to explain the EEG.

Methods

Patient selection-All patients were obtained from the University of Chicago neonatal intensive care unit, and were born from 29 to 38 week gestation. Patients were selected among those who had undergone an EEG as part of a clinical evaluation. None of the patients were receiving CNS active medications, none had seizures, none had intra-ventricular hemorrhage and none (retrospectively) had significant neurological problems. All of the EEGs were interpreted as normal. The majority of infants were being screened as part of an apnea evaluation. Similar criteria were applied to older infants (greater than 3 years of age) who were obtained from the records of the routine ambulatory EEG laboratory.

Segment Selection- EEG segments were selected by scrolling through the record and selecting the first 30 sec. epoch in which the patient's state was clear and free of artifacts. Three replications of wakefulness were selected. The segments were each 30 seconds in duration, sampled at 400 Hz, filtered from 1 to 70. The electrodes chosen for analysis were from the neonatal modified 10-20 system – Fp1, T3, T4 O1.

EEG Analysis- Measures included correlation dimension, Kolmogorov entropy, eigenstructure and a normalized measure of non-linearity (z). Time delays and embedding dimension were data adaptive and the entropy measures are noise corrected.

Algorithms -The estimation of the non-linear variables was based on attractor reconstruction. The state of the system (i.e. the brain) that generates the EEG or ECoG can be represented by a projection of all variables in a multi-dimensional state space. The EEG signal consists of sampled data; in the state space , two points of the sampled time series with an inter-distance of k sampled points are plotted against each other, thus showing the relationship between the values of samples i and i + k. In general, if there is no relationship between the points in a time series (e.g. a random signal), one expects the points to be distributed evenly over the space. Takens [9] proved that the dynamic state of a system could be reconstructed from a time series generated by the system, by using time delay coordinates.

The technique can be described in a general fashion as embedding a time series x_1, x_2, x_3, ..x_N into a set of vectors X_i with m elements:

$$X_i = (x_i , x_{i+k} , x_{i+2k} , \ldots, x_{i+(m-1)k})^T \qquad (1)$$

where k is the delay in number of samples and T is the epoch of the time series embedded in the vector. The value of T should not be too large so that the first and last values in the epoch are practically uncorrelated. On the other hand, T should be large enough to cover the dominant frequency in the time series. We determined the embedding parameters following the procedures described by Schouten et al [7]. We use a delay k equal to unity, therefore the number of dimensions (m) in the time window T is determined by the sample frequency of the EEG (400 samples/s). The number of vectors (i) determines the total length of the time series required for the attractor reconstruction procedure. Our time series of N points were normalized by subtracting the mean ($x_m = [1/N] \Sigma x_i$) and dividing by the average absolute deviation dx:

$$dx = [1/N] \Sigma | x_i - x_m| \qquad (2)$$

The number of crossings of the mean divided by two was used as an estimate for the number of cycles (N_{cycles}). The value of m was chosen as the rounded value of N/N_{cycles}. Using these criteria, our values for m varied between 45 and 200, close to the recommended values (50-200) by Schouten et al [7]. To obtain sufficient vectors X_i as the basis for estimation of the non-linear metrics, the total number of points per reconstruction was set to 12000 (30 s of EEG).

One of the variables that can characterize an attractor is entropy [2]. Entropy estimates the rate at which information about the state of the system is lost. Order-2 Kolmogorov Entropy can be estimated by examination of two initially close orbits on an attractor, and measuring the time (t) required for the orbits to diverge beyond a set distance ε. One could present it as an index of chaos in the signal. For example, entropy of a static system is zero, noise has infinite entropy, and chaotic systems have entropy between the two extremes. The distribution of the time intervals f(t) satisfies:

$$f(t) \sim e^{-KE.t} \qquad (3)$$

where KE is the Kolmogorov entropy. Using the property in (3) and based on the maximum norm, Schouten et al [6] developed a computationally efficient maximum-likelihood estimator for KE, which we have incorporated in our studies.

A commonly used characterization is the correlation dimension. Calculation of this metric is based on the correlation integral [1]:

$$C(s) = \{1/(N.(N-1))\} \Sigma\, \Theta(s - |\, X_i - X_j \,|) \qquad (4)$$

With Θ = Heaviside step function, and N = the number of points. The term $|\, X_i - X_j \,|$ denotes the distance between the points in state space. The distance between points in space may be evaluated with the Euclidian norm or the maximum norm; in terms of dimension, the results obtained with the two techniques are equivalent. The value of C(s) is a measure of the number of pairs of points (X_i, X_j) on the reconstructed attractor whose distance is smaller than s. Because the correlation integral counts the pairs of closely related points in the plot, the distribution of the points over the space is characterized for the attractor. The values of s are data dependent in the sense that they are scaled by the average absolute deviation (equation 2) between dx/400 and dx/100. If N approaches infinity and s approaches zero in equation (4), C(s) scales according to a power law $C(s) \sim s^D$, where D is the correlation dimension of the attractor.

In addition to the non-linear metrics, a linear one was extracted. The largest eigenvalue (Ei) of the time series was determined with a principal component analysis (PCA). The largest eigenvalue indicates the amount of variance explained by the first principal component. By monitoring Ei, we evaluate existence and contribution of a dominant component around the occurrence of a seizure. The eigenvalue gives us one relative measure of the system's behavior that is explained by linear metrics [5].

To test the non-linearity of the data, the recorded time series were compared with surrogate data sets. The test is based on creating surrogate data series with the same power spectrum as the original signal but with no phase correlation [3]. Surrogate data sets were introduced as a precautionary measure against the over-zealous search for low dimensional chaos. The surrogate time series, which yields the same power spectrum and autocorrelation as the original time series, was obtained by the inverse transform of the phase randomized Fourier spectrum. The growth of inter-point distances was used as the statistic to test the null hypothesis whether the original could be described by linearly correlated noise [10]. From comparisons between the original and surrogate series, a quantity z was calculated from the Mann-Whitney U rank-sum statistic. By comparing the recorded data with 50 surrogate sets, a mean value of z can be obtained. The z-value is normally distributed with zero mean and unit variance. While it is not our intent to determine whether the EEG is a low dimensional chaotic system, if the non-linearity index is low we are especially cautious in our interpretation of more specific non -linear tests.

The algorithms for data-conversion, and the wave editing process were implemented in MatLab (The Math Works Inc., Natick, MA). The largest eigenvalue and the variables based on non-linear dynamics were calculated with a software package developed for the analysis of time series that include noise [8].

Results

Examples of raw waveforms are shown in Fig. 1. A generalized linear analysis of variance fixed effects model was used (electrode x age) for data analysis. The significance level was fixed for all of the comparisons, at $p<0.01$. The means are shown in Table 1.

There were no significant differences for the correlation dimension for age or electrode position. For the Kolmogorov entropy, the effect of age and electrode were significant. The neonates had a lower KE than the older children (KE of 37 versus 21 for the children and infants, respectively). The KE also showed a significant electrode effect, with the temporal leads showing the highest values for KE for both age groups.

The eigenvalues also showed significant overall age dependency (.54 versus .74 for the children versus newborns, respectively). There was no significant effect of electrode position for eigenvalues, although the mean for the frontal electrode was highest among the four positions.

Our surrogate (z), used to determine if the data set is consistent with various linear systems, also showed a large age dependant change (-.91 versus –2.90 for the children versus neonates, respectively). Finally, there was an electrode effect, due to the fact that the frontal electrode had a higher z than other electrodes.

The relationships amongst the measures is consistent. As the eigenvalue decreases, with increasing age, the Kolmogorov entropy increases. There is a similar inverse relationship between KE and the eigen value for electrode position, also. The relationship between the values of z and KE and eigen value are more complex. As the eigen value decreases with age, z decreases and KE increases.

Discussion

While knowledge of the development of single unit behavior and cell-cell interactions has advanced at a steady pace, relatively little is known regarding the development of population or large neural network responses. In part, this is due to a weakness in the conceptual framework, but also hampered by the paucity of analytical tools available for characterizing large network behavior. Given the large number of variables that influence brain development, that these factors interact with one another in rather complex ways and that the cellular activity underlying the population behavior is known to be non-linear, it is not surprising that analytical tools derived from dynamical systems analysis are under evaluation. The overall outcome of this study provides encouragement for the continued application of dynamical systems analysis tools to characterizing the development of the human EEG. Reliable responses were obtained from even the youngest population-neonates. Additionally, Kolmogorov entropy (KE), eigenvalues and surrogate based measures of non-linearity (z) all showed large and consistent age dependant changes. These measures were also sensitive to regional differences in brain development.

There is only one prior article to which we can compare our results, and then only for the correlation dimension. Meyer-Lindenberg [4] described the evolution of the CD, Lyapunov exponent and non-linearity as measured using surrogate data analysis. The CDs for frontal, temporal and occipital leads were 4.0, 4.0 and 3.8 in the Meyer-Lindenberg study [4] versus 3.6, 4.3, and 4.0 for our neonatal group. Large differences were seen in the older age group 6.1, 7.7, and 7.7 versus our results of 4.2, 4.5 and 4.2. The methods for calculating the CD were different in the two studies (e.g. embedding, dimension, tau, number of samples, etc) and the data selection and editing process was clearly different. We selected samples without eye movement contamination and specified patient state, while the earlier study used an autoregressive technique for removing the artifact and state was not an explicit variable.

The results of our study in the older age group are consistent with the frequent observation that normal EEG segments taken from neurologically normal adults have only modest evidence of nonlinearity. This is clearly not the case in the newborn where z was frequently greater than –3.0. Inspection of raw waveforms clearly demonstrates the dramatic differences in the appearance of the waveforms as a function of age. The discontinuities seen in the premature and term infant recordings are compelling, and never seen in normal older patients. The presence of discontinuities shows non-stationarity. Hence, we use entropy and correlation dimension only in an informal sense. The eigenvalues showed a clear age dependency. The older population had lower eigenvalues.

Finally, the age dependency for KE was quite large. Clearly KE increases with age, nearly doubling over the age range in this study. The biological significance of the increase in entropy with age is not yet clear. As entropy increases, the number of possible states of the system increases and the “information” loss is higher. Whether the increasing state possibilities are directly related to the maturation of anatomic connectivity, as a function of age, requires direct verification. Nevertheless, we are encouraged to continue to use KE as an index of complexity of the EEG signal and are continuing to investigate whether the KE may prove more sensitive than CD in the pediatric population. This is directly relevant to the application of seizure detection and anticipation algorithms.

Acknowledgment

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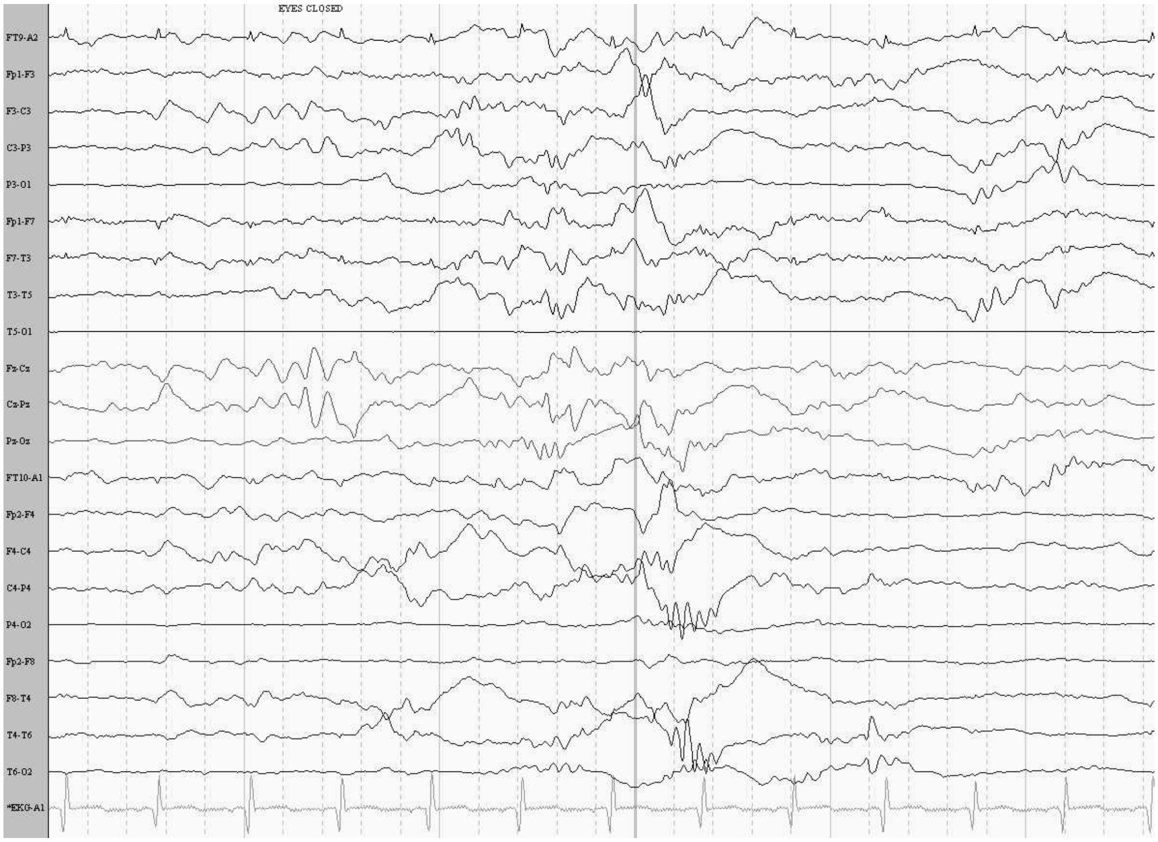
Table 1. Means of Dynamical Systems Measures

	CD	KE	z	Eigen value
Neonates	**4.0**	**21**	**-2.90**	**.74**
Children	**4.3**	**37**	**-.91**	**.54**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F3-C3
C3-P3
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T3-T5
T5-O1
Fz-Cz
Cz-Pz
Pz-Oz
FT10-A1
Fp2-F4
F4-C4
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F8-T4
T4-T6
T6-O2
*EKG-A1

Fig. 1A

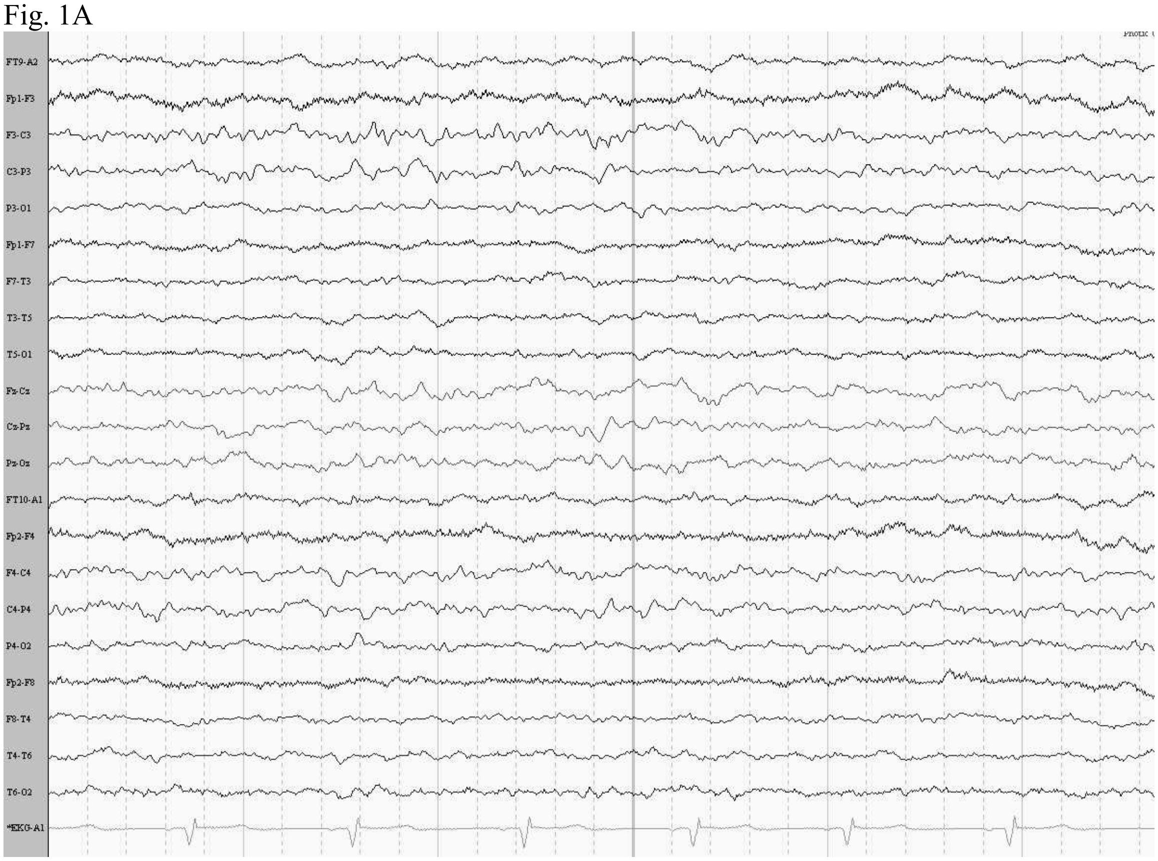
FT9-A2
Fp1-F3
F3-C3
C3-P3
P3-O1
Fp1-F7
F7-T3
T3-T5
T5-O1
Fz-Cz
Cz-Pz
Pz-Oz
FT10-A1
Fp2-F4
F4-C4
C4-P4
P4-O2
Fp2-F8
F8-T4
T4-T6
T6-O2
*EKG-A1

Fig. 1B