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Nonlinear dynamical analysis of the neonatal EEG time series: The relationship between neurodevelopment and complexity

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Abstract

Objective: To investigate the relationship between the complexity of sleep EEG time series and neurodevelopment for premature or full-term neonates.
Methods: Nonlinear dynamical analysis of neonatal sleep EEG time series is used to compute the correlation dimension D_2 which is an index of the complexity of the dynamics of the developing brain. The dimensional complexity is estimated using Theiler's modification of the Grassberger–Procaccia algorithm for two different values of Theiler's w parameter. The hypothesis that neonatal EEG data during sleep contains nonlinear features is verified by means of surrogate data testing.
Results: The dimensional complexity of the neonatal EEG increases with neurodevelopment and brain maturation. There is furthermore a statistically significant difference between the dimensional complexity of the EEG for neonates born prematurely when compared to full-term neonates at the same postmenstrual age (PMA). The neonatal EEG time series data used in this study proved to contain nonlinear features where the 'null hypothesis' of surrogate data testing is rejected with $p \ll 0.0001$.
Conclusions: A relationship between neurodevelopment and brain maturation and the complexity of the dynamics of the brain as measured by the dimensional complexity of the sleep EEG time series has been established. In particular, the dimensional complexity tends to increase with neurodevelopment and maturation as indicated by their PMA and birth status (premature or full-term). In particular, the brain dynamics of neonates born prematurely is less complex than the brain dynamics of neonates born full-term even at the same PMA. We attribute this to differences in the neurodevelopment between these two cohorts. We propose that the dimensional complexity can be used as an index for quantifying neurodevelopment.
Significance: The dimensional complexity as measured by the correlation dimension of the sleep EEG time series may potentially be a useful measure for quantifying neurodevelopment in neonates. Future work is directed at the analysis of other EEG channels to understand the relationship between complexity in different regions of the brain and maturation and neurodevelopment, along with the utility of complexity to relate to neurodevelopment at older ages as measured by the Bayley score.
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Keywords: Neurodevelopment; Neonate; EEG sleep; Nonlinear dynamics; Grassberger–Procaccia algorithm; Correlation dimension; Dimensional complexity

1. Introduction

Nonlinear dynamical analysis techniques such as the correlation integral and dimension (Grassberger and Procaccia, 1983a,b), Lyapunov exponents, etc. have recently gained interests from a number of fields of research, especially in the analysis of human EEG (Pritchard and Duke,

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1995). Nonlinear dynamical analysis has been applied to various types of EEG time series including data obtained for both normal and abnormal clinical situations (Stam and Pritchard, 1999).

Temporal patterns of the EEG have been shown to provide insight into the various functional states of neural networks in the brain (Stam and Pritchard, 1999). In this regard, nonlinear dynamical analysis of the EEG can elucidate features of the brain dynamics that are associated with different normal and abnormal functional states. Nonlinear dynamical analysis when used properly provides complementary information to classical linear time series analysis leading to a deeper understanding of the brain dynamics associated with different functional states.

Among the available methods of nonlinear dynamical analysis, the correlation integral $C(r)$ using the Grassberger–Procaccia algorithm is the most common method applied to EEG time series analysis (Pritchard and Duke, 1995), especially for sleep EEGs (Ferri et al., 2002). Furthermore, the correlation dimension (D_2) computed using the Grassberger–Procaccia algorithm is the easiest dimension to compute (Pritchard and Duke, 1995), although the computational time required can be prohibitive and careful selection of the computational parameters as well as interpretation of the results are necessary.

In the calculation of the correlation integral using the Grassberger–Procaccia algorithm, there are however two primary requirements to obtain reliable results: the stationarity of the time series (Eckmann and Ruelle, 1985; Theiler, 1986) and the length of the stationary time series, i.e., $N \geqslant 10^d$ where d is the correlation dimension (D_2) of the time series. It is rather difficult to satisfy (or verify) such requirements when dealing with real time series data, especially for the EEG time series because long epochs of sleep EEG generally contain nonstationary components (Röschke and Aldenhoff, 1992; Fell and Röschke, 1994; Fell et al., 1996) and there are generally an insufficient number of data points in shorter epochs to provide good estimates of D_2. The parameters in the calculation of the correlation integral and the estimation of the correlation dimension also need to be chosen carefully to ensure accurate and reliable computational results. The most important parameters in correlation dimension estimation are the embedding parameters, i.e., the embedding dimension (m) and the time delay (τ) (Theiler and Rapp, 1996). Different values of data acquisition parameters including sampling rate, analog-to-digital conversion precision and digital filtering can have a significant effect on the estimated correlation dimension of a given time series (Pritchard and Duke, 1995), thereby making comparisons between results often difficult, if not impossible.

If a nonlinear dynamical system has a low-dimensional chaotic attractor (Eckmann and Ruelle, 1985), the correlation dimension (D_2) is defined as the exponent v at small distances r such that the correlation integral $C(r)$ has a power-law characteristic. This exponent can be estimated as the slope of the log–log plot between $C(r)$ and r (Grassberger and Procaccia, 1983a) and, as such, quantifies the active degrees of freedom or the complexity of the dynamical system on the attractor. Therefore the working hypothesis when using the correlation integral in the analysis of an EEG time series is that the neuronal networks in the brain that generate spontaneous EEG have a low-dimensional attractor and the estimated correlation dimension (D_2) can be used to quantify the complexity of the brain as a dynamical system on this attractor.

The brain as a complex dynamical system, however, appears to contain both high-dimensional processes and low-dimensional processes. There is general agreement on the idea (Ferri et al., 2002) that the EEG is generated by a high-dimensional process which cannot be distinguished, on the basis of currently available methods, from noise (Rombouts et al., 1995; Theiler and Rapp, 1996; Stam et al., 1999). High dimensionality may be related to EEG desynchronization that is probably the consequence of weakly coupled oscillations of neuronal networks with out-of-phase frequencies (Ferri et al., 2002); on the contrary, low dimensionality may be the direct result of EEG synchronization potentially resulting from a self-organizing process that switches uncoordinated neuronal activity to coupled oscillations (Ferri et al., 2002).

There is also another controversy regarding the use of nonlinear dynamical analysis methods in the study of EEG. The questions that emerge are related to whether or not the EEG time series contains nonlinear features and does an estimate of the correlation dimension (D_2) provide a measure of the nonlinear dynamic characteristics of the neural networks in the brain? The method of surrogate data testing introduced by Pijn et al. (1991) and Theiler et al. (1992a,b) and refined in many subsequent works (Schreiber and Schmitz, 1996; Schreiber, 1998) has been proposed to help answer these questions through statistical tests that can be used to distinguish between a nonlinear dynamic process and a linear stochastic process. Surrogate data are a randomized time series derived from the original data that have the same power spectra and amplitude distribution as the actual data (Stam et al., 1999). If there is a statistically significant difference between the computational results of the original time series and the surrogate data time series, the 'null hypothesis' that the original time series can be described by a stochastic linear model can be rejected (Theiler et al., 1992a,b; Stam et al., 1999). In addition, Theiler (1986, 1990) revised the Grassberger–Procaccia algorithm by adding a new parameter called the Theiler window w. The Theiler window is intended to correct for autocorrelation effects of the time series which can result in underestimation of the correlation dimension.

Accordingly, the computation of the dimensional complexity of an EEG time series using the Grassberger–Procaccia algorithm may not yield an accurate estimate of the correlation dimension (D_2). However, such a measure obtained using the Grassberger–Procaccia algorithm may still be useful for making relative comparisons among groups of interest (Pritchard and Duke, 1995). The mea-

sure thus serves as a relative index of the complexity of the brain dynamics (Pritchard and Duke, 1995) and the result of the computation using the Grassberger–Procaccia algorithm is then referred to as the dimensional complexity (DCx) (Pritchard and Duke, 1995) rather than the correlation dimension (D_2). The term dimensional complexity (DCx) is used in this study.

One of the first applications of nonlinear dynamical analysis of the EEG time series was the work by Babloyantz et al. (1985) where the correlation dimension (D_2) was computed using the Grassberger–Procaccia algorithm (Grassberger and Procaccia, 1983a) and the relationship between correlation dimension and different stages of sleep was investigated. Subsequently, several similar studies (e.g. Gallez and Babloyantz, 1991; Röschke, 1992; Röschke and Aldenhoff, 1991; Röschke et al., 1993; Fell et al., 1993), were carried out using the correlation dimension and Lyapunov exponents. From these studies, supporting results that was consistent with Babloyantz et al., 1985 were reported where the correlation dimension (D_2) and the largest Lyapunov exponent (L_1) decreased with sleep stage changes in adults from stage I to stage IV (Stam and Pritchard, 1999). In addition, consistent results were also obtained from the correlation dimension (D_2) of a study conducted over the entire night of sleep (Ackermann et al., 1994a,b).

Using the technique of surrogate data testing, evidence of nonlinear features in spontaneous normal EEG was found for a large number of subjects using inferential statistical testing by Pritchard et al. (1995), Rombouts et al. (1995), and Meyer-Lindenberg (1997). On the other hand, some studies reported that it was not possible to distinguish an EEG time series from a linear stochastic time series (e.g. Glass et al., 1993; Palus, 1993). The revised algorithm of Grassberger–Procaccia proposed by Theiler to deal with autocorrelation effects in a time series (Theiler, 1986, 1990) was used by Theiler and Rapp (1996) to re-examine the human EEG time series that were examined in Rapp et al. (1989). In this study, they did not find low-dimensional behavior as reported in the previous study.

This is the first paper of a two-paper series that addresses nonlinear dynamical analysis of the neonatal sleep EEG time series. In this first paper, the relationship between neurodevelopment and maturation of neonatal subjects is examined using the dimensional complexity of their brain dynamics as measured through the analysis of spontaneous EEG. In the subsequent paper (Janjarasjitt et al., revised version under review), the dimensional complexity corresponding to different sleep stages is investigated. The dimensional complexity is estimated using the revised Grassberger–Procaccia algorithm (Theiler, 1986, 1990). In this study, two different values of the Theiler window w are used and the dimensional complexity of the surrogate data derived from the neonatal EEG time series is also determined using both values of the Theiler window w used in the analysis of the actual neonatal EEG time series.

From the results of this study, we concluded that there is a direct relationship between neurodevelopment and dimensional complexity. The dimensional complexity tends to increase with neurodevelopment and brain maturation. This tendency is an expected feature with neurodevelopment in healthy subjects. Secondly, we show that neonates who were born premature are more likely to have less complex brain dynamics as quantified using dimensional complexity than those neonates who were born full-term even at the same PMA. Finally, because the 'null hypothesis' of the surrogate data tests can be rejected with statistical significance, it can be concluded that the neonatal sleep EEG data used in this study contain nonlinear features that are quantifiable using dimensional complexity.

2. Methods

2.1. Data and Subjects

The cohort studied included 50 healthy neonates composed of 22 males and 28 females with gestational ages that range from 28 weeks to 42 weeks (34.12 ± 5.96 weeks). Here the healthy status of the neonates refers to no ventilatory care and the absence of sepsis, seizures, intracranial hemorrhage and metabolic disturbances such as acidosis. Further, all neonates recruited for this IRB-approved study had Brazy Scores equal to zero and consent forms were obtained for all subjects. Electroencephalographic/polysomnographic studies were performed in an environmentally controlled setting in which sound, light, humidity, and tactile stimulation were monitored. All neonates were studied while sleeping prone or on their sides in an open bed, whichever was their usual sleeping position in the nursery. Continuous recordings began after a diaper change and feedings at approximately 9:00 PM, and ended at approximately 9:00 AM the following morning. The entire 24-channel recording was digitized on a Hewlett Packard workstation (Palo Alto, CA, USA), with the first 3 h of the study simultaneously recorded on paper using a 21-channel electroencephalographic machine (Nihon Kohden, Model 4221, Sunnyvale, CA, USA). Fourteen channels of bipolar EEG recording consisting of Fp1-T3, T3-O1, Fp2-T4, T4-O2, Fp1-C3, C3-O1, Fp2-C4, C4-O2, T3-C3, C3-C7, Cz-C4, C4-T4, Fz-Cz and Cz-Pz were obtained using the standard 10–20 EEG lead system. The neonatal sleep EEG data were recorded with a 12-bit A/D converter and a sampling rate of 64 Hz. Prior to acquisition the EEG data were filtered using a first-order low-pass filter with cut-off frequency of 35 Hz and a first-order high-pass filter with a time constant of 0.30 s, 0.53 Hz. The high-pass filter should effectively eliminate the influence of low frequency REM artifact in the acquired EEG. The sampling frequency of 64 Hz with an antialiasing low-pass filter with cut-off at 35 Hz leaves the potential for aliasing in the acquired EEG signal. Additional low-pass filtering with a cut-off of 29 Hz is used to eliminate artifact due to undersampling.

In this study, the subjects were categorized into two main groups according to the gestational age of the subjects: preterm (PT) and full-term (FT). There were 28 preterm subjects and 22 full-term subjects. Further, the preterm subjects were divided into two subgroups according to the PMA of the subjects at the time of the study: polysomnographic recordings of the preterm subjects that were performed at birth are referred to as PT0 and polysomnographic recordings of the preterm subjects that were performed at a PMA equivalent to the gestational age of a full-term neonate are referred to as PT1. The terminology and definition of age during the perinatal period used in this study are as given by Fetus and Newborn (2004), see Fig. 1.

Eighty-six polysomnographic recordings were performed with PMAs that range from 28 weeks to 43 weeks (36.44 ± 4.62 weeks). One study was performed for each of the full-term subjects at birth (22), while serial studies (64) were performed on the preterm subjects with a minimum of two studies each. Digitized neurophysiologic data for each minute of sleep during the recording were compared with the contemporaneous minute of EEG sleep, and neonates were visually assigned one of six sleep states according to conventional neonatal EEG sleep criteria (Pope et al., 1992) for the full-term subjects, i.e., two active and two quiet sleep states as well as indeterminate and waking states. Minutes for the sleep study of the preterm subjects were scored either as continuous or discontinuous EEG, with the degree of discontinuity scored as records of quiescence during each minute. However, the complexity of one-minute epochs of the EEG data is analyzed independent of visually scored sleep state designation.

2.2. Analytic framework

Only channel Fp1-C3 of the neonatal sleep EEG data is analyzed in this study, analysis of all the other channels will be reported in a subsequent publication. The dimensional complexity of one-minute epochs of the neonatal EEG time series is determined using the Grassberger–Procaccia algorithm with Theiler's modification and values of the Theiler window $w = 1$ and $w = 15$. In addition, the dimensional complexity of one-minute epochs of the surrogate time series derived from the neonatal EEG time series is also determined to verify the evidence of nonlinearity in the neonatal EEG time series. Correspondingly, the surrogate data of PT0, PT1, and FT are denoted by SPT0, SPT1, and SFT, respectively. The embedding parameters used in the calculation of the correlation integral were the embedding dimension $m = 14$ and the time delay $\tau = 2$. The embedding parameters, m and τ, that are used in this study are chosen by using the false nearest neighbor method (Kennel et al., 1992) and the mutual information technique (Fraser and Swinney, 1986), respectively. The average number of false neighbors of the EEG time series significantly drops to nearly zero around the embedding dimension $m = 14$. The time delay $\tau = 2$ is chosen based on the fact that the mutual information of the EEG time series decreases to less than $1/e$ at around $\tau = 2$. Furthermore, the Theiler window $w = 1$ is used for the standard Grassberger–Procaccia algorithm, while the value of Theiler window $w = 15$ is chosen so that the Theiler window exceeds the embedding dimension m.

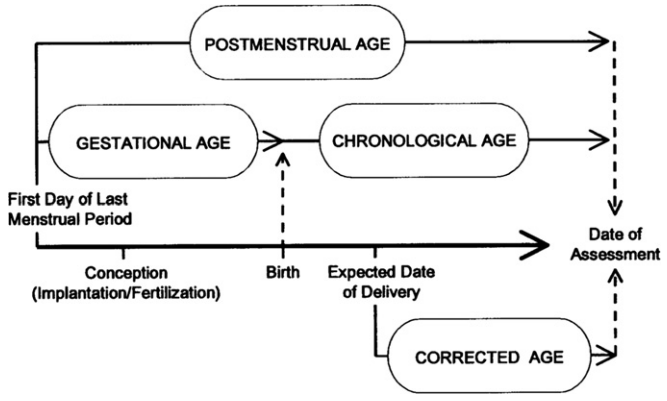

Fig. 1. Diagram of the age terminology during perinatal period recommended by Committee on Fetus and Newborn (Fetus and Newborn (2004)).

In this study, we analyzed the dimensional complexity of the neonatal sleep EEG time series corresponding to the neurodevelopment and maturation of the neonatal study groups, i.e., PT and FT. We examined the results of the dimensional complexity in four fundamental aspects. In Study I, we use dimensional complexity to assess neurodevelopment of all subjects based only on their PMA and not their birth status. In Study II, we evaluate the dimensional complexity of the neonatal subjects at birth to study the relationship between neurodevelopment, dimensional complexity and gestational age. Then the dimensional complexity of the preterm neonates is investigated in Study III and, in Study IV, the dimensional complexity of the neonatal groups PT0, PT1 and FT is analyzed to study the relationship between birth status, PMA, and dimensional complexity as a measure of quantifying neurodevelopment and brain maturation.

2.3. Correlation integral and dimension

The estimation algorithm used in this paper for computation of the correlation dimension D_2 and estimating the dimensional complexity is composed of two basic steps (Pritchard and Duke, 1995). In the first step, the attractor of the nonlinear system is reconstructed from the univariate time series using a time-delay embedding, also referred to as the Takens reconstruction (Takens, 1981). In step 2, the correlation dimension of the reconstructed attractor is estimated from the correlation integral. The commonly used method for estimating the correlation dimension, such as in the nonlinear analysis of EEG (Pritchard and Duke, 1995), is the Grassberger–Procaccia algorithm (GPA) (Grassberger and Procaccia, 1983b,a).

2.3.1. Attractor reconstruction

Given a univariate time series $\{x[0], x[1], \ldots, x[N-1]\}$ where each sample $x[n]$ is a one-dimensional (observed) measure of the nonlinear system that is being analyzed. To provide a more complete description of the higher dimensional nonlinear system, the time series x needs to be unfolded into a higher dimension space called the embedding space by using a time-delay embedding scheme as, for example, given in Packard et al. (1980). The m-dimensional embedding vector $\mathbf{x} \in \mathscr{R}^m$ of the time series x is given by (Theiler, 1990)

$$\mathbf{x}[n] = (x[n]x[n+\tau]\cdots x[n+(m-1)\tau])^{\mathrm{T}} \tag{1}$$

where $n = 0, 1, \ldots, N_e - 1$, $N_e = N - (m-1)\tau$, and m and τ are the embedding parameters denoting the embedding dimension and the time delay, respectively, and T denotes vector transpose. This time-delay embedding technique unfolds the observed time series into an m-dimensional embedding space and provides a more comprehensive representation of the behavior of the higher dimensional nonlinear system on the attractor. The topological results of Takens (1981) and Mañé (1981) indicate that if $m > 2v$ where v is the dimension of the system on the attractor, the original state space of the system is reconstructed from the time-delay embedding of the observed time series (almost everywhere). This choice of embedding dimension provides a sufficient condition for attractor reconstruction, where in Hilborn and Ding (1996) it is shown that unfolding of the attractor is accomplished with $m = v$ for almost all systems.

Although almost any time delay τ and embedding dimension $m > v$ will in principle work with infinitely precise data (Theiler, 1990), it is nontrivial to choose the embedding parameters in an optimal way for real time series data. For example (Theiler, 1990), at any given embedding dimension m, if the time delay τ is too large, then the elements $x[n]$ and $x[n+(m-1)\tau]$ of the reconstructed state vector $\mathbf{x}$ will be effectively decorrelated and this will result in over estimation of the correlation dimension. On the other hand, if the time delay τ is too small, then the elements $x[n], \ldots, x[n-(m-1)\tau]$ will be highly correlated (or dependent) to each other and the reconstructed attractor will have a shape similar to a diagonal hyperplane. It is also inefficient to take τ to be small because the elements of the reconstructed state vector $\mathbf{x}$ will not be independent (Theiler, 1990).

The important parameter for time-delay embedding is neither the embedding dimension m nor the time delay τ separately but the embedding window w_τ (Albano et al., 1988) that depends on both embedding parameters, i.e., $w_\tau = (m-1)\tau$. It has been suggested that the measurements of a chaotic system are most sensitive to the time delay τ for sufficiently large embedding dimension m (Kaplan and Glass, 1992, 1993). There are a number of methods for determining the time delay τ such as the autocorrelation function (Albano et al., 1988), mutual information (Fraser and Swinney, 1986), higher-order correlation (Albano et al., 1991), average displacement (Rosenstein et al., 1994), etc. A sufficient embedding dimension m can be determined by using the false nearest neighbor technique (Kennel et al., 1992), for example.

2.3.2. Correlation integral and dimension calculation

The correlation integral $C(r)$ of the nonlinear time series $x[n]$ is defined by (Grassberger and Procaccia, 1983b,a)

$$C(r) = \lim_{N_c\to\infty} \frac{2}{N_c} \sum_{i=0}^{N_e-1} \sum_{j=i+1}^{N_e-1} \Theta(r - \|\mathbf{x}_i - \mathbf{x}_j\|) \tag{2}$$

where $N_c = N_e(N_e-1)$ and the Heaviside function $\Theta(n) = 1$ if $n \geqslant 0$; 0 otherwise. A revised algorithm was introduced by Theiler (1986, 1990) to correct for autocorrelation effects in the time series by using the Theiler window w. Theiler's modified algorithm is defined by (Theiler, 1986, 1990)

$$C(r) = \lim_{N_c\to\infty} \frac{2}{N_c} \sum_{i=0}^{N_e-1} \sum_{j=i+w}^{N_e-1} \Theta(r - \|\mathbf{x}_i - \mathbf{x}_j\|) \tag{3}$$

where $N_c = (N_e - w)(N_e - w + 1)$ and w denotes the Theiler window. According to Grassberger and Procaccia (1983a), the correlation integral $C(r)$ behaves as a power of v for small r, that is,

$$C(r) \propto r^v. \tag{4}$$

The exponent v is defined as the correlation dimension D_2 and can be calculated by

$$v = \lim_{r\to 0} \frac{\log(C(r))}{\log(r)}. \tag{5}$$

In this study, the correlation dimension v is determined from the estimate of the local slope of the correlation integral $C(r)$ using the estimation scheme presented in Borovkova (1998).

The surrogate data used in this study were generated to preserve the amplitude distribution of the time series while minimizing any changes to the second-order statistics of the time series, i.e., the autocorrelation function and PSD. The surrogate data are constructed from the original time series data using the iteratively refined surrogate method (Schreiber and Schmitz, 1996).

3. Results

3.1. Dimensional complexity of neonatal sleep EEG time series Study I

The effect of age-related neurodevelopmental changes in subjects as measured by dimensional complexity independent of birth status, i.e., preterm or full-term, is examined. The dimensional complexities of all 86 studies using Theiler windows $w = 1$ and $w = 15$ are, respectively, shown in Figs. 2 and 3. For the boxplots shown in these and subsequent figures, the middle bar in each box specifies the median dimensional complexity of the group, the box

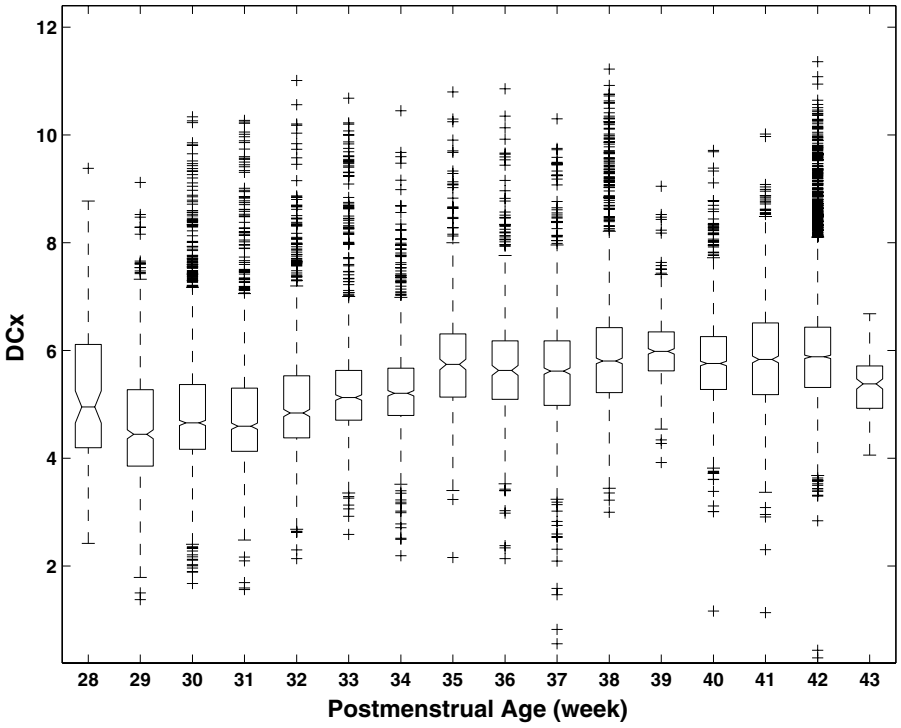

Fig. 2. Correlation between postmenstrual age and dimensional complexity of Study I with Theiler window $w = 1$.

represents one quartile of the dimensional complexities of the group, the length of each whisker is equal to 1.5 quartiles of the dimensional complexities of the group, and the "+" marks represent outliers. If the notches in the boxplots do not overlap, then the medians of the dimensional complexities of the two groups being compared are significantly different with 95% confidence.

When the Theiler window w is changed from $w = 1$ which is the Grassberger–Procaccia algorithm to $w = 15$, the dimensional complexity of the EEG time series

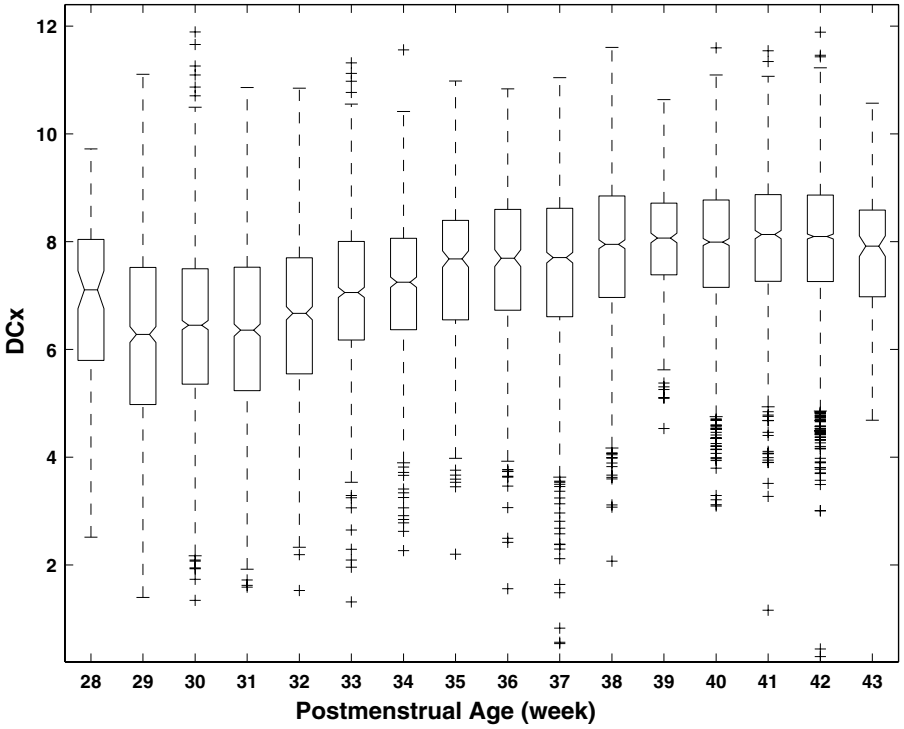

Fig. 3. Correlation between postmenstrual age and dimensional complexity of Study I with Theiler window $w = 15$.

increased overall. In general, the dimensional complexity increases with neurodevelopment and maturation as the PMA increases. This suggests that more mature neonates tend to have more complex brain dynamics than less mature neonates.

3.2. Dimensional complexity of neonatal sleep EEG time series Study II

The complexity of the EEG time series of neonates at birth is determined. The dimensional complexities of 45 studies including both subjects that were born preterm and full-term are computed with Theiler window $w = 1$ and illustrated in the box plots shown in Fig. 4. Clearly, the dimensional complexity is increasing with the gestational age of the neonate at birth. This suggests that the dynamics of the neuronal system is becoming increasingly complex with neurodevelopment and maturation during the gestational period.

The dimensional complexity of the same subjects is determined using the Theiler window $w = 15$ and, as expected, the dimensional complexity increases when compared to the case when the Theiler window $w = 1$, this is illustrated in Fig. 5. The dimensional complexity of neonates is still increasing with gestational age at birth.

3.3. Dimensional complexity of neonatal EEG sleep time series Study III

The dimensional complexity of preterm neonates is analyzed corresponding to their PMA. The dimensional complexity at various PMAs is computed for Theiler window $w = 1$, shown in Fig. 6, and for Theiler window $w = 15$, shown in Fig. 7. Also, there is a tendency for the dimensional complexity to increase as the PMAs of the preterm neonates increase for both Theiler windows $w = 1$ and $w = 15$.

3.4. Dimensional complexity of neonatal EEG sleep time series Study IV

Now we examine the dimensional complexity of the neonatal EEG time series during sleep in terms of the subject groups, i.e., PT0, PT1, and FT. The dimensional complexity of PT0, PT1, and FT is compared in Figs. 8 and 9 where the Theiler windows are $w = 1$ and $w = 15$, respectively. In addition, the median, mean, and standard deviation (SD) of the dimensional complexities of these three cohorts using $w = 1, 15$ are summarized in Table 1. The FT cohort has the highest dimensional complexity while the dimensional complexity of PT1 is higher than the dimensional complexity of PT0.

From the two-tail, paired t-test of the dimensional complexities between PT0 and PT1, between PT0 and FT, and between PT1 and FT, the null hypothesis of all tests can be rejected. Therefore, based on the two-tail, paired t-tests, the results suggest that there are statistically significant differences between the dimensional complexities of PT0 and PT1, between the dimensional complexities of PT0 and FT, and between the dimensional complexities of PT1 and FT with a p-value of $p \ll 0.0001$ as given in Table 2.

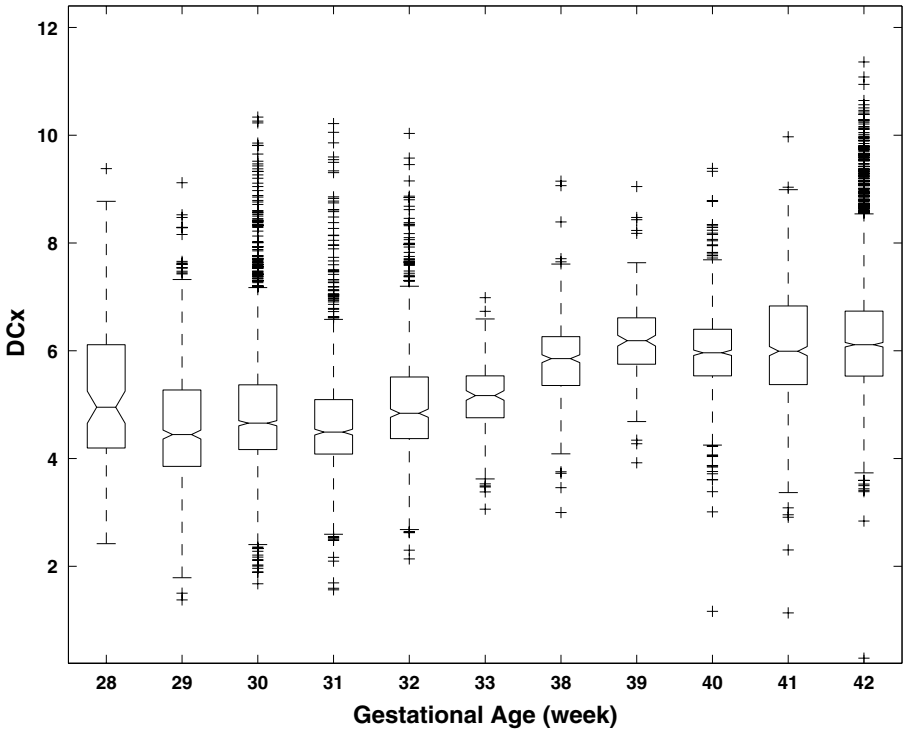

Fig. 4. Correlation between postmenstrual age and dimensional complexity of Study II with Theiler window $w = 1$.

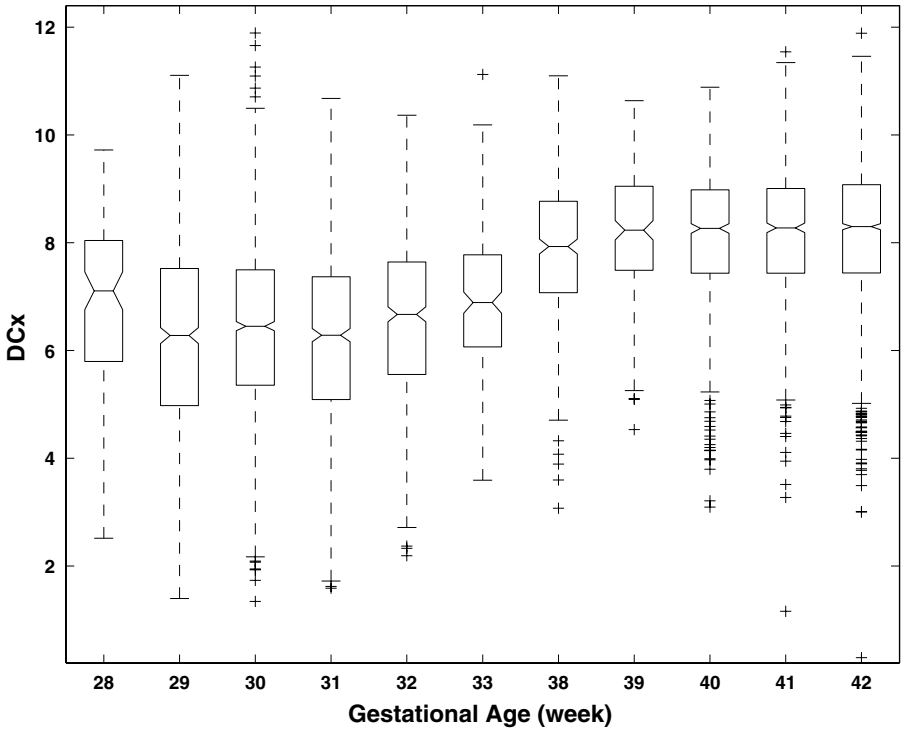

Fig. 5. Correlation between postmenstrual age and dimensional complexity of Study II with Theiler window $w = 15$.

3.5. Dimensional complexity of surrogate data of neonatal EEG sleep time series

The dimensional complexity of the surrogate data of the neonatal sleep EEG time series of all 86 studies using Theiler windows $w = 1$ and $w = 15$ is, respectively, illustrated in Figs. 10 and 11. The tendency of the dimensional complexity to increase with neurodevelopment as observed in our analysis of the original data is not clearly exhibited in the surrogate data. The dimensional complexity at vari-

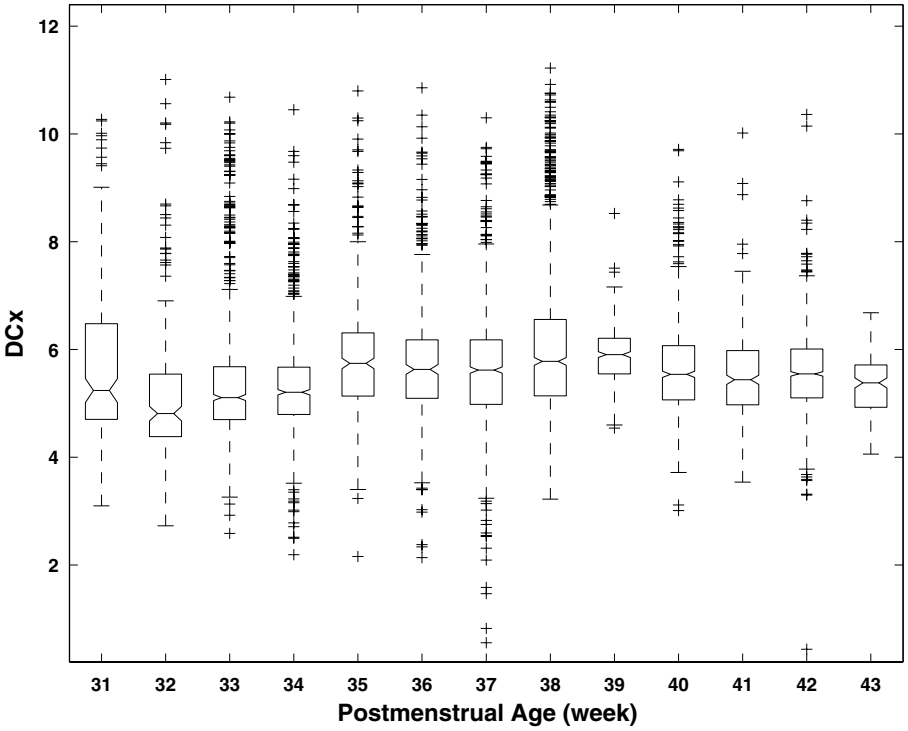

Fig. 6. Correlation between postmenstrual age and dimensional complexity of Study III with Theiler window $w = 1$.

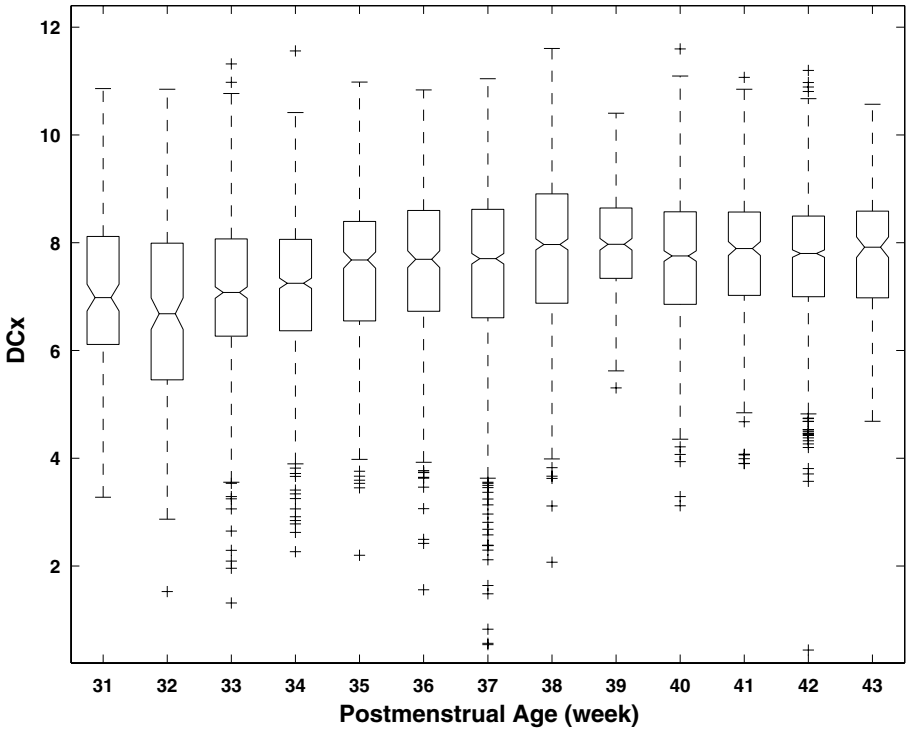

Fig. 7. Correlation between postmenstrual age and dimensional complexity of Study III with Theiler window $w = 15$.

ous stages of neurodevelopment and maturation as measured by PMA is approximately the same.

In terms of the subject groups, the dimensional complexity of SPT0, SPT1, and SFT using Theiler window $w = 1$ is shown in Fig. 12, while Fig. 13 compares the dimensional complexity of SPT0, SPT1, and SFT using Theiler window $w = 15$. The median, mean, and standard deviation of the dimensional complexities of SPT0, SPT1, and SFT using $w = 1, 15$ are also summarized in Table 1.

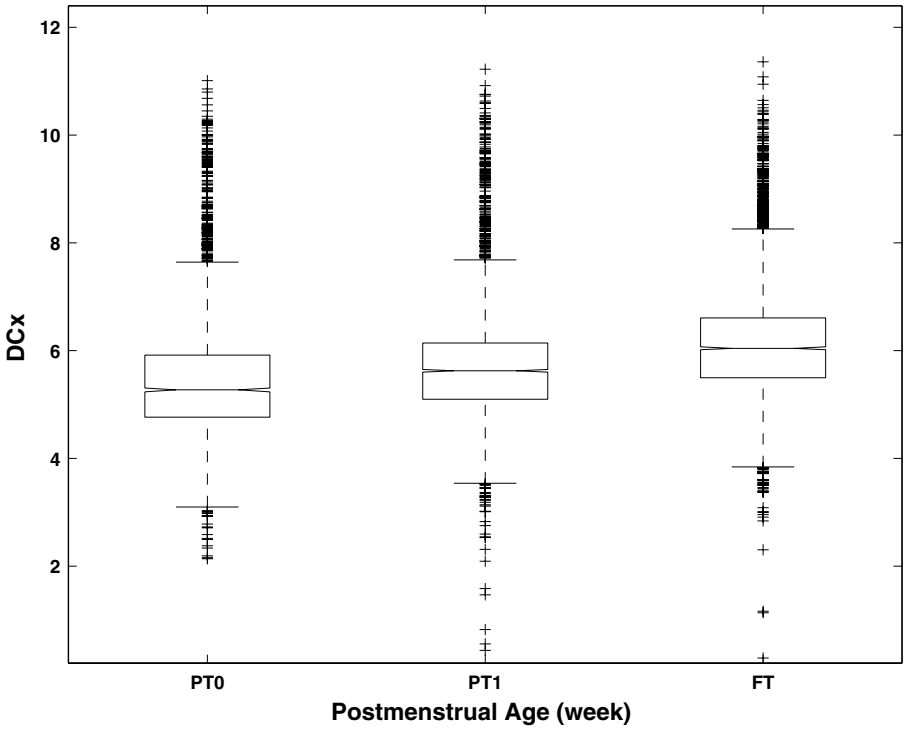

Fig. 8. Comparison of the dimensional complexity of Study IV with Theiler window $w = 1$.

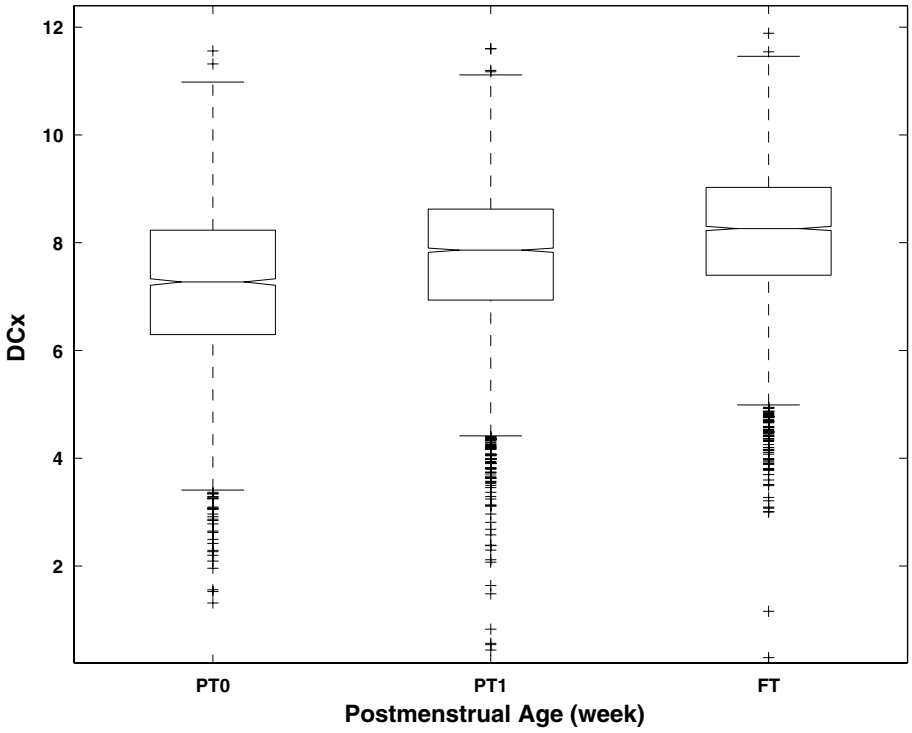

Fig. 9. Comparison of the dimensional complexity of Study IV with Theiler window $w = 15$.

From this analysis we can conclude that the neonatal sleep EEG time series has quantifiable nonlinear features because the dimensional complexities of the original neonatal sleep EEG data are significantly different from the dimensional complexities of the surrogate data for all subject groups. In fact, the results of the two-tail, paired t-tests applied to the means of the various groups with a p-value of $p \ll 0.0001$ are shown in Table 3.

4. Discussion

This paper has provided a detailed analysis of the relationship between the dimensional complexity of an EEG time series and brain maturation in healthy neonates, for a given region of the brain. Using a conventional measure of dimensional complexity, correlation dimension, we have demonstrated that from a single channel ($F_{p1}C_3$) of neonatal EEG during sleep, there is a statistically significant relationship between the dimensional complexity of this neonatal sleep EEG time series and the neurodevelopment (brain maturation) of the subjects studied. This work builds on our earlier efforts (Scher et al., 2005) where we also investigated the role of correlation dimension in assessing brain maturation and neurodevelopment in the same cohort. The motivation for the results presented in this paper was to increase our understanding of what temporal features in the EEG time series were actually being measured and quantified by the dimensional complexity metric, and to seek refinements of these nonlinear calculations that can provide more rapid and efficient estimates of complexity which can be applied to bedside diagnostic and therapeutic interventions.

Other groups have applied nonlinear time series analyses to study brain maturation in the child from EEG recordings. For example, correlation dimension calculated from waking EEG increased with age from neonatal to adult-

Table 1
Dimensional complexities corresponding to the subject groups

Subject	w	Median of DCx	Mean of DCx	SD of DCx
PT0	1	5.2707	5.5035	1.2366
PT1	1	5.6243	5.6911	1.0064
FT	1	6.0412	6.1723	1.1165
PT0	15	7.2698	7.1898	1.4717
PT1	15	7.8594	7.7147	1.3369
FT	15	8.2616	8.1308	1.2716
SPT0	1	6.6025	6.8703	1.2982
SPT1	1	5.8802	6.1228	1.2328
SFT	1	6.2433	6.4979	1.2757
SPT0	15	8.7918	8.7132	1.0494
SPT1	15	8.1837	8.1297	1.1550
SFT	15	8.4995	8.4756	1.0705

Table 2
Results of two-tail, paired t-test of dimensional complexities between the subject groups

DCx1	DCx2	w	Hypothesis	p
PT0	PT1	1	Reject H_0	< 0.0001
PT0	FT	1	Reject H_0	$\ll 0.0001$
PT1	FT	1	Reject H_0	$\ll 0.0001$
PT0	PT1	15	Reject H_0	$\ll 0.0001$
PT0	FT	15	Reject H_0	$\ll 0.0001$
PT1	FT	15	Reject H_0	$\ll 0.0001$

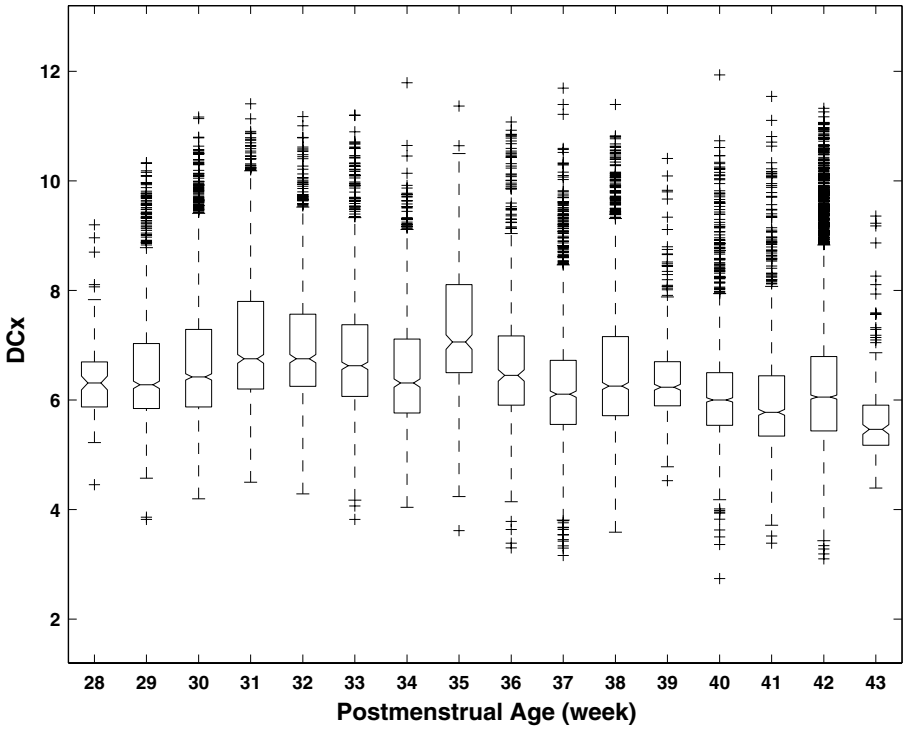

Fig. 10. Correlation between postmenstrual age and dimensional complexity of the surrogate data for all studies with Theiler window $w = 1$.

hood (Meyer-Lindenberg, 1996). These same trends were documented in neonatal cohorts of increasing postmenstrual ages during active and quiet sleep (Scher et al., 2005; Pereda et al., 2006). Nonlinear methods have also been used to estimate the interdependence among EEG signals from multiple brain regions in both adult subjects (Pereda et al., 2001; Terry et al., 2004), as well as in neonates (Pereda et al., 2003). Recently, investigators have shown that the overall interdependence among brain regions in healthy neonates evolves from nonlinear to linear expressions with

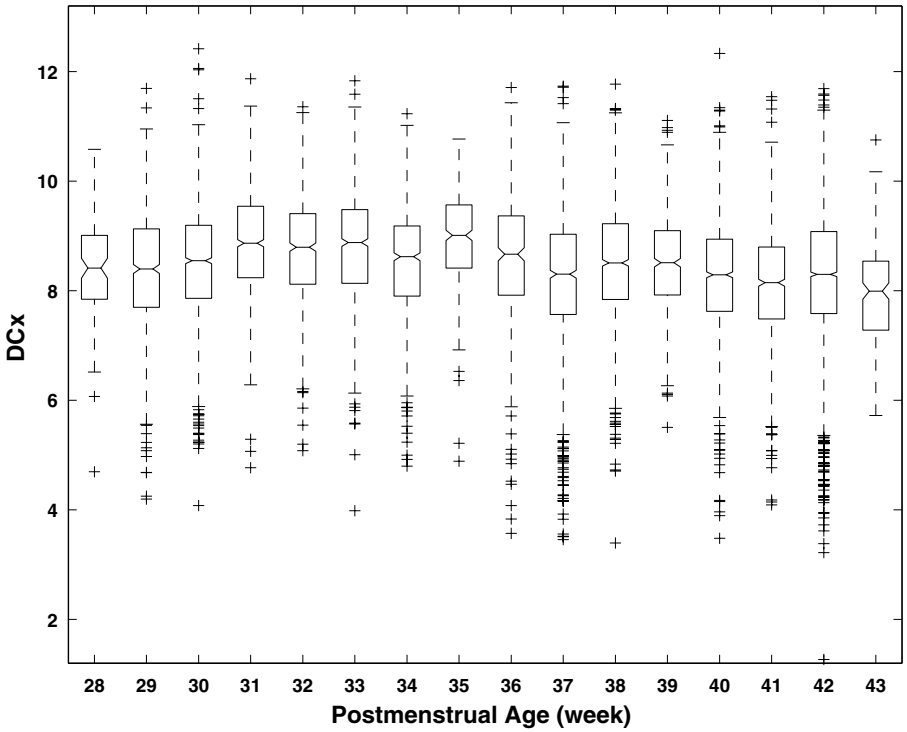

Fig. 11. Correlation between postmenstrual age and dimensional complexity of the surrogate data for all studies with Theiler window $w = 15$.

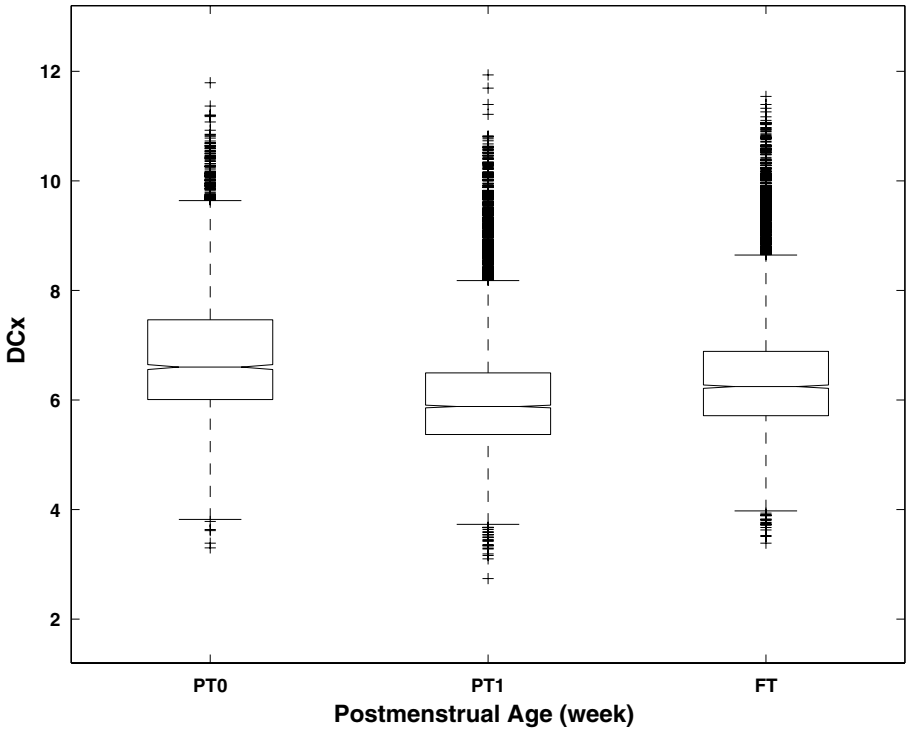

Fig. 12. Comparison of the dimensional complexity of the surrogate data corresponding to the subject groups with Theiler window $w = 1$.

increasing postmenstrual ages during quiet sleep (de la Cruz et al., 2007). These authors also stress that changes in the overall linear correlations in the beta band during active and quiet sleep may help in predicting long-term brain maturation.

It is well understood that the computation of dimensional complexity using the correlation dimension can be confounded by linear stochastic temporal processes in the time series, whether they are inherent in the signal being measured or the result of the measurement process. As

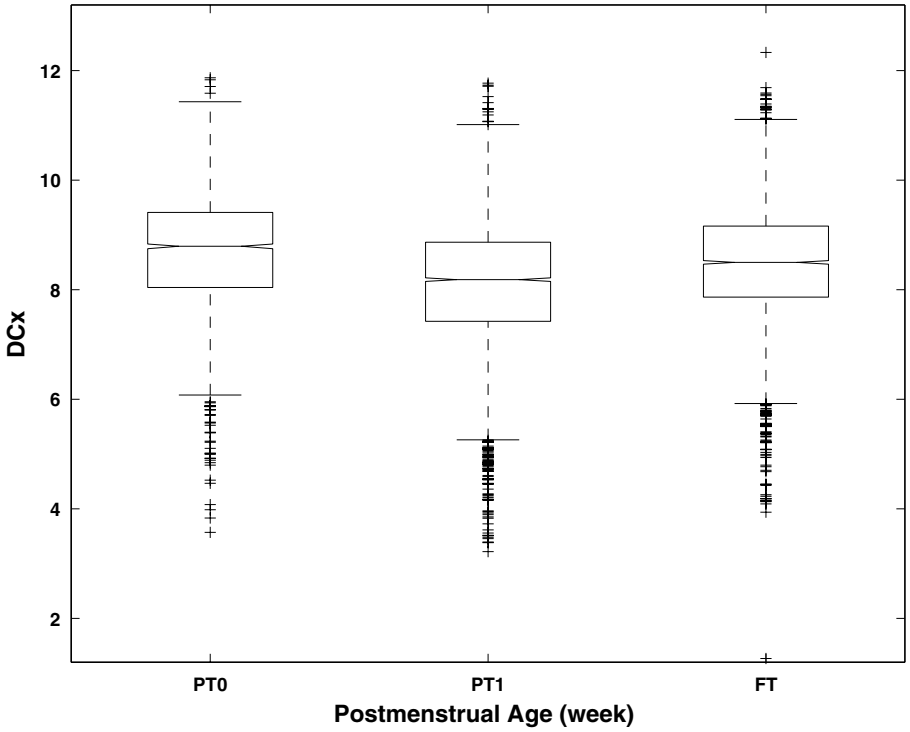

Fig. 13. Comparison of the dimensional complexity of the surrogate data corresponding to the subject groups with Theiler window $w = 15$.

Table 3
Results of two-tail, paired t-test of dimensional complexities between the actual data and their surrogate data

DCx1	DCx2	w	Hypothesis	p
PT0	SPT0	1	Reject H_0	$\ll 0.0001$
PT1	SPT1	1	Reject H_0	$\ll 0.0001$
FT	SFT	1	Reject H_0	$\ll 0.0001$
PT0	SPT0	15	Reject H_0	$\ll 0.0001$
PT1	SPT1	15	Reject H_0	$\ll 0.0001$
FT	SFT	15	Reject H_0	$\ll 0.0001$

such, there has been speculation in the EEG community that linear methods of analysis are sufficient to characterize the signal properties of spontaneous EEG that may be important in a clinical setting. Hence, we extend our previous results in this paper using a more thorough analysis including surrogate data methods in conjunction with hypothesis testing and statistical analysis to conclude that dimensional complexity can be used as a measure of brain maturation and neurodevelopment where increased complexity is associated with increased development as quantified by gestational and postmenstrual ages. Our subsequent work will include analysis using data from additional EEG channels to help improve understanding of the spatial distribution of dimensional complexity, and if this information can be integrated with results from imaging studies, this combined data may provide the information necessary to connect the signal analysis results with maturational changes that are occurring in the underlying neural networks of the brain.

We comment that the slope of the $\log(C(r))$ versus $\log(r)$ curve derived from the neonatal sleep EEG time series, referred to in our work as the dimensional complexity, may not precisely be the correlation dimension. Recall, the correlation dimension as introduced in the original work of Grassberger and Procaccia quantifies the active degrees of freedom of a nonlinear dynamical system on its attractor, and is a measure of the exponent of the power-law relationship that is valid for this system on an appropriate scaling region. The correlation dimension has been accurately determined for a variety of synthetic systems such as the Lorentz and Rossler systems, but because of potential confounding effects as mentioned above, the true correlation dimension of real-world data cannot be accurately confirmed. However, this may not be as significant a problem as it seems at the outset. In particular, as shown in this paper the dimensional complexity is a useful measure that can be used to quantify temporal aspects in the neonatal EEG time series and further provides some insightful information related to the dynamics of the neural networks in different maturational states. Even though we cannot unequivocally establish that the dimensional complexity is equal to the "true" correlation dimension of the times series being analyzed, the fact that dimensional complexity can provide a measure of the complexity of the brain dynamics as measured through the EEG time series and that this measure is intrinsically linked to neurodevelopment and maturation, which may be of clinical utility, should not be ignored.

Motivation for the application of both linear and nonlinear quantitative analyses of EEG resides in the ability to more completely characterize EEG signals that are not apparent by visual analysis (Scher et al., 2005). Reduced dimensional complexity for specific groups of high-risk neonates may help predict later functional deficits at older ages as reflected in structural changes of magnetic resonance images studies in children and adolescents (Isaacs et al., 2000; Peterson et al., 2000; Hüppi et al., 1996; Cooke and Abernethy, 1999). Combined use of quantitative EEG and neuroimaging tools may also offer insights into developmental neural plasticity from both a functional and structural point of view (Als et al., 2003).

In conclusion, we recognize the limitations of nonlinear approaches to time series analysis and have used surrogate data testing methods to evaluate the validity of our results, and we have also used caution in the interpretation of our results in the context of well-established nonlinear system terminology. Surrogate data testing is essential to assess the validity of the results as compared to conclusions derived from data analyses from EEG recordings. Other problems that are faced include the intrinsic nonstationarity of the EEG data, where the epoch length of the data must be chosen to meet the conflicting requirements of the computational algorithms being used in terms of the number and stationarity of the data samples. Further, the effects of intrinsic and extrinsic linear stochastic signal features can confound many of the nonlinear signal analysis methods, so caution and care must be used in both the computation and interpretation of the results. Finally, although we have demonstrated the utility of dimensional complexity of a single channel of EEG in quantifying maturational and neurodevelopmental changes in a healthy neonatal cohort, further work is needed to extend this analysis to other EEG channels in this cohort, integrating other EEG features both linear and nonlinear into the analysis using discriminant analysis methodologies, investigating the ability of these features both singularly and in combination to predict neurodevelopmental outcome in this cohort at 9, 18 and 27 months as measured by the Bayley scores available in our data set, and then extending this work to include at-risk neonates who have been monitored and studied as a part of a clinical protocol at Rainbow Babies and Children's Hospital, Case Academic Medical Center, Cleveland, OH.

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