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FULL-LENGTH ORIGINAL RESEARCH

Real-time differentiation of nonconvulsive status epilepticus from other encephalopathies using quantitative EEG analysis: A pilot study

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Summary

Purpose: Distinguishing nonconvulsive status epilepticus (NCSE) from some nonepileptic encephalopathies is a challenging problem. In many situations, NCSE and nonepileptic encephalopathies are indistinguishable by clinical symptoms and can produce very similar electroencephalography (EEG) patterns. Misdiagnosis or delay to diagnosis of NCSE may increase the rate of morbidity and mortality.

Methods: We developed a fast-differentiating algorithm using quantitative EEG analysis to distinguish NCSE patients from patients with toxic/metabolic encephalopathy (TME). EEG recordings were collected from 11 patients, including 6 with NCSE and 5 with TME. Three nonlinear dynamic measures were used in the proposed algorithm: the maximum short-term Lyapunov exponent (STLmax), phase of attractor (phase/angular frequency), and approximate entropy (ApEn). A further refined metric derived from STLmax and phase of attractor (the mean distance to EEG epoch samples from their centroid in the feature space) was also utilized as a criterion. Paired *t* tests were carried out to further clarify the separation between the EEG patterns of NCSE and TME.

Results: Computational results showed that the performance of the proposed algorithm was sufficient to distinguish NCSE from TME. The results were consistent in all subjects in our study.

Conclusions: The study presents evidence that the maximum short-term Lyapunov exponents (STLmax) and phase of attractors (phase/angular frequency) can be useful in assisting clinical diagnosis of NCSE. Findings presented in this article provide a promising indication that the proposed algorithm may correctly distinguish NCSE from TME. Although the exact mechanism of this association remains unknown, the authors suggest that epileptic activity is highly associated with and can be modeled by dynamic systems.

KEY WORDS: Epilepsy, EEG, Nonconvulsive status epilepticus, Nonlinear dynamical measures, Toxic/metabolic encephalopathy.

Nonconvulsive status epilepticus (NCSE) is usually defined as an epileptic state lasting 30 min or more with some clinically evident change in mental status or behavior (unless comatose) associated with ictal activity on electroencephalography (EEG) (Brenner, 2002). Nonconvulsive seizures during NCSE do not contain convulsive motor activity and may be repeated discrete seizures or more continuous prolonged seizures.

NCSE is particularly difficult to diagnose in patients presenting with stupor or coma as there are often little or no specific clinical symptoms. Misdiagnosis or delay to diagnosis of adult NCSE may engender morbidity and

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mortality (Bearden et al., 2008). Often, the diagnosis of NCSE requires an EEG recording to be performed and then examined by an expert (Towne et al., 2000; Bearden et al., 2008). The prevalence of EEG study in NCSE has been addressed in several large epidemiologic studies. An EEG study of 236 patients concluded that 8% of comatose patients without clinical seizure activity had NCSE that would not likely have been diagnosed without EEG recording (Towne et al., 2000). Another study of 570 consecutive patients undergoing continuous EEG monitoring revealed that 19% of these patients had seizures and 92% of these seizures were nonconvulsive (Claassen et al., 2004).

Most EEG patterns of NCSE are generalized epileptiform waves or focal rhythmic ictal transformations that are not difficult to identify as electrographic seizure activity (Geiger & Harner, 1978). However, in some cases, diagnosis of NCSE can be difficult because of the presence of other disorders with similar EEG waveforms (Brenner, 2002). In particular, some nonepileptic encephalopathies, such as toxic/metabolic encephalopathy (TME), are indistinguishable by clinical symptoms, and may produce EEG patterns similar to those seen during NCSE. Some of these equivocal EEG patterns are generalized triphasic-like waves or diffuse semi-rhythmic delta activity (Fig. 1A,B).

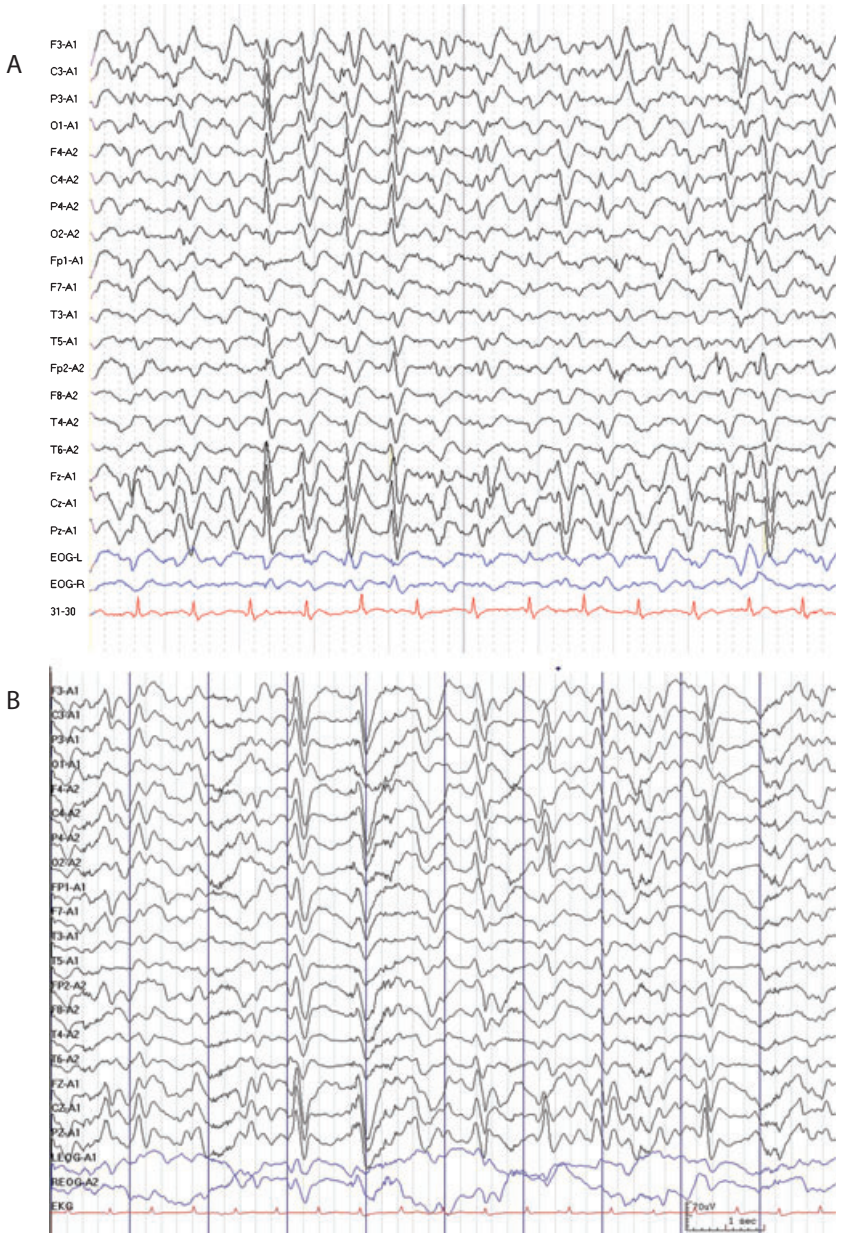

Figure 1.
Ten second electroencephalography (EEG) recordings of (**A**) an equivocal pattern of nonconvulsive status epilepticus (NCSE) (triphasic "like" waves), from a 68-year-old male patient with subdural hematoma, who began having focal NCSE, which evolved into generalized NCSE; (**B**) a 10-s EEG recording of triphasic waves in a 56-year-old male patient with toxic/metabolic encephalopathy (TME) with severe acute liver failure. Visual similarities regarding the triphasic waves of TME and triphasic "like" waves of NCSE are profound.
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Treatment with benzodiazepines (BZDs) can reduce electroencephalographic seizure activity and/or improve clinical state, which may be useful diagnostically. However, the diagnostic utility of BZDs can be limited because BZDs may transiently suppress triphasic waves due strictly to metabolic encephalopathy as well as triphasic-like waves seen during NCSE (Fountain & Waldman, 2001). Furthermore, NCSE and TME can coexist, and at present, combining clinical judgment and experience is the only effective method to diagnose NCSE in equivocal cases (Bearden et al., 2008).

Although the possibility of NCSE causing irreversible damage to the brain is still debated, rapid diagnosis and treatment of NCSE is desirable as untreated NCSE often leads to further medical complications and temporary brain damage (Jirsch & Hirsch, 2007; Drislane et al., 2008). In the past, quantitative EEG analysis has been investigated as an aid in diagnosis of some psychiatric and neurologic disorders (Pardalos et al., 2004; Thulasidas et al., 2006; Liu, 2008). One approach to expedite diagnosis would be to introduce a real-time EEG-based classification algorithm.

The purpose of this study is to identify EEG characteristics (used during bedside real-time EEG recording or during postrecording analysis) that can distinguish NCSE from nonepileptic encephalopathy. This may assist physicians in generating a more rapid diagnosis of NCSE or nonepileptic encephalopathy. In our study, data-mining algorithms are applied to extract complex and intrinsic features from large datasets in multichannel EEG recordings, since the EEG patterns of NCSE can be visually similar to those of nonepileptic encephalopathy.

Methods

Data description

Quantitative analysis was performed on EEG recorded from male and female adult patients having been diagnosed with generalized NCSE or with a nonepileptic encephalopathy, specifically TME in this study. The clinical classification of the patients into the above-mentioned two categories was performed by an experienced epileptologist (B.U.) who reviewed the clinical history of the patient, EEG findings, and other testing results, along with response to anticonvulsants (if administered). Eleven subjects were involved in this study, in which six were diagnosed with NCSE, and the other five were diagnosed with TME. The EEG recording length of patients with NCSE ranges from 25–63.8 min (mean ± standard deviation 38.60 ± 16.10), whereas the EEG recording length of patients with TME ranges from 13.00–56.16 min (mean ± standard deviation: 27.66 ± 16.57).

EEG recordings were acquired using the international 10–20 electrode placement. For each subject, there are 21 recording channels (Fp1, Fp2, F3, F4, C3, C4, A1, A2, P3, P4, O1, O2, F7, F8, T3, T4, T5, T6, Fz, Cz, and Pz). None of the subjects had any signs of convulsive motor activity during the recordings.

An effective approach in order to shed light into the underlying nonlinear structure of time series in our case EEG recordings, is analysis in the state space (also known as phase space). In this approach, EEG recordings are mapped from the time domain onto an n dimensional state space, which is defined by the method of delays (Takens, 1981).

If we consider the time series signal x(t) (row vector of length m), we can construct the m by n matrix $A = [x(t)^T, x(t+\tau)^T, \ldots, x(t+(n-1)\tau)^T]$ (where τ is the delay parameter and n is the embedding dimension). Then, every line (row) of the matrix A can be seen as a point on the n dimensional space. In this way we can construct the so-called attractor of the signal. In the analysis of dynamic systems the attractor is a useful visualization tool of the signal because it can reveal structure and patterns that are well hidden in the time domain. In order to quantify state changes and attractor geometric patterns, one can employ several well-defined nonlinear dynamic measures. For the purpose of our study we used three such measures, namely:

(1) *The maximum short-term Lyapunov exponents (STLmax)* are a state-space–based nonlinear measure that quantifies the instability of a dynamic system. The maximum short-term Lyapunov exponents have been used extensively in nonlinear EEG analysis, mostly for seizure prediction (Wolf et al., 1985; Iasemidis et al., 1990, 2001, 2004, 2005).

(2) *Phase of the attractor*, also called angular/frequency phase, estimates the rate of change of the stability for a dynamic system. Complementing to Lyapunov exponents, angular/frequency phase is a broadly used state-space–based nonlinear measure that is employed to characterize chaotic systems.

(3) *Approximate entropy (ApEn)* is another phase space statistic that quantifies the complexity of a dynamic system (Kolmogorov, 1958; Pincus, 1991, 1995; Kaplan et al., 1991).

Mathematical descriptions of these measures can be found in the Appendix S1.

In order to analyze the continuous EEG recordings, we segmented the whole time series into epochs of a finite time window of 10.24 s at a sample rate of 250 Hz. For each 10.24-s epoch, values for STLmax, phase of attractor, and ApEn were computed. Points were plotted in a three-dimensional space (should not be confused with the n dimensional embedding space used for calculating the three measures).

Plots of the three nonlinear dynamic measures show very good separation between patients with NCSE and patients with TME. In Fig. 2 we can see the scatterplot of the three dynamic measures (using EEG recordings in a

single channel for an NCSE patient and a TME patient). X axis, Y axis, and Z axis correspond to ApEn, phase of attractors, and STLmax, respectively.

The formation of two clearly distinct and well-separated clouds of points led us to suggest an automated algorithm for real-time identification of NCSE based on the centroids and mean radius of the clouds, defined by the three-dimensional scatterplot points. We define as the centroid of N points (x_i, y_i, z_i) i = 1, 2, …, N the point with coordinates:

$$c_N = (x_c, y_c, z_c) = \left(\frac{1}{N}\sum_{i=1}^{N} x_i, \frac{1}{N}\sum_{i=1}^{N} y_i, \frac{1}{N}\sum_{i=1}^{N} z_i \right) \quad (1)$$

The mean Euclidean radius distance of the N-point cloud is:

$$\overline{d_N} = \frac{1}{N}\sum_{i=1}^{N} \sqrt{(x_c - x_i)^2 + (y_c - y_i)^2 + (z_c - z_i)^2} \quad (2)$$

In order for each of the features to contribute equally, all three (x, y, z) features are normalized in scale [0, 1]. Based on these, the real-time algorithm can be described in the following steps:

(1) Every 10.24 s compute one point on the three-dimensional space spanned by the three nonlinear measures;
(2) Update the centroid and the mean radius distance using Eqns 1 and 2 correspondingly;
(3) If the centroid coordinates do not change more than a predefined quantity ε, issue diagnosis based on the last centroid coordinate.

Results

Analysis carried out in the whole dataset (11 patients, 21 EEG channels) shows results similar with the preliminary example in Fig. 2. In Fig. 3 one can see a cumulative scatterplot with the three nonlinear dynamic measures for all the 11 patients plotted together, using 21-channel averages in the three-dimensional feature space. Although the cloud of points is very dense, one can see that there is clear separation between the two classes.

We further observed that STLmax and phase of attractor play a major role in this separation, whereas ApEn contributes very little. This makes it possible to quantify the subject profile by using only two features.

We then computed metrics described in Eqns 1 and 2. First, for each patient we computed the centroid, taking into consideration epoch samples generated from all 21 EEG channels and using the full length of the EEG recording available.

For the generalized NCSE patients, the numerical values of centroids were 0.0800 ± 0.0261 for STLmax, 0.1433 ± 0.0175 for phase of attractor, and 0.5567 ± 0.0565 for ApEn. For the TME patients, the numerical values of centroids were 0.4700 ± 0.1700 for STLmax, 0.4080 ± 0.1139 for phase of attractor, and 0.5300 ± 0.0374 for ApEn.

These results verify that the features that contribute the most toward the separation of NCSE and TME are STLmax and phase of attractor. This implies that generalized NCSE can be identified with even fewer (two, instead of three) dynamic measures and less computational effort.

Next, for each patient, the mean distance from the already recorded EEG epochs to their centroid in the feature space is computed, as defined by Eqn 2. In Fig. 4, for each patient the evolution curve of the mean distance is plotted. After 20 min of EEG recording, the mean distances of the NCSE patients all drop below 0.06, converge, and stay there, whereas the mean distances of the TME patients do not converge rapidly and remain above 0.08 after starting EEG recording for a while. This

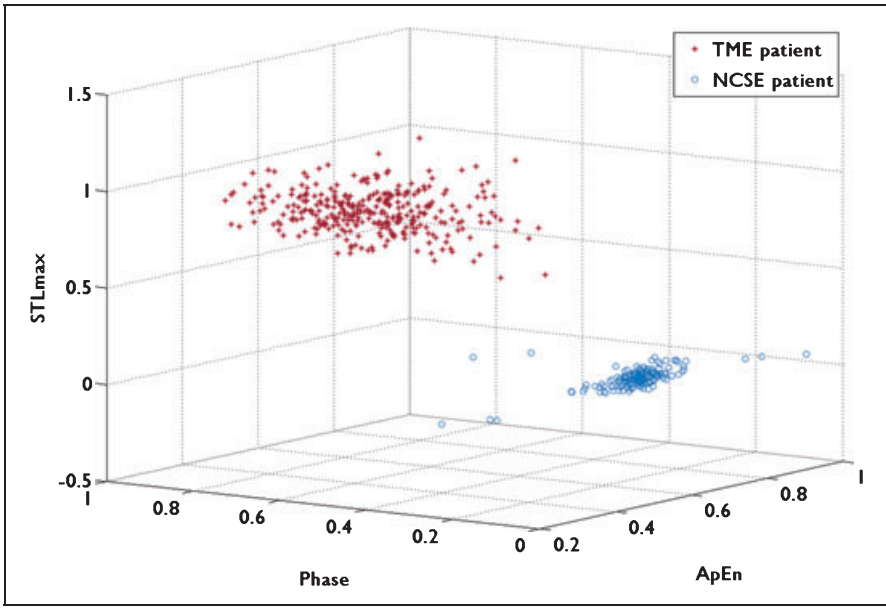

Figure 2.
Scatterplot of the three nonlinear dynamic measures (1. ApEn, 2. phase of attractor, 3. STLmax; already normalized) for a patient with toxic/metabolic encephalopathy (TME) and a patient with generalized nonconvulsive status epilepticus (NCSE). Each circle or star corresponds to a 10.24-s epoch. This example shows electroencephalography (EEG) epochs from recordings of a single channel.
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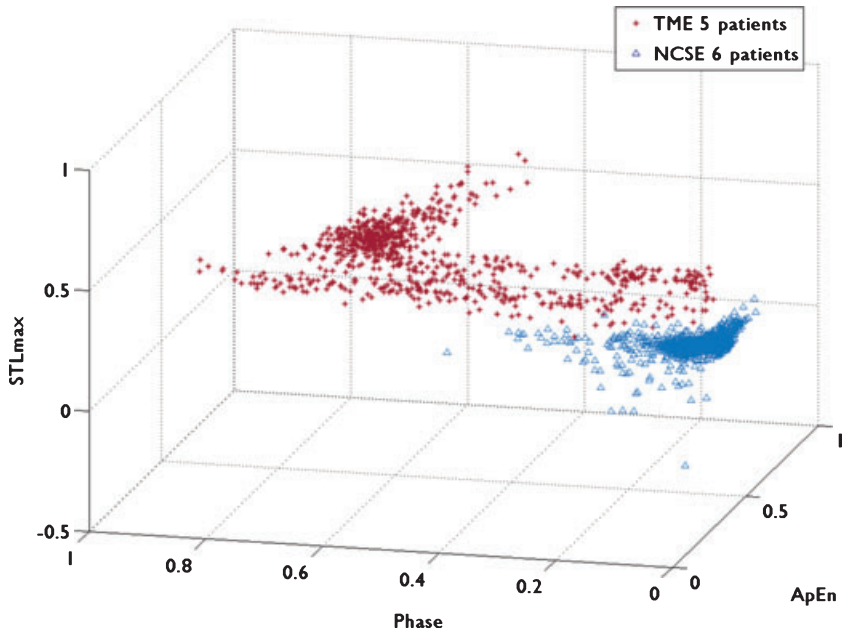

Figure 3.
Nonlinear dynamic measures (1. STLmax, 2. phase of attractor, 3. ApEn; already normalized) for all 11 human subjects plotted together, using the average of 21 channels. Every circle or star corresponds to a 10.24-s electroencephalography (EEG) epoch sample.
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indicates that, in the feature space, epoch samples of generalized NCSE are more concentrated than those of TME. The difference can be used as an effective criterion to judge whether a patient should be classified into generalized NCSE or TME.

The computation of the centroids and mean distances to the centroids (Fig. 4) already indicated that the STLmax and phase of attractor are sufficient to separate these two classes of patients. We then performed a statistical *t* test in order to further justify this observation.

For each of the three nonlinear dynamic measures (STLmax, phase of attractor, and ApEn), paired *t* tests are implemented on all the six generalized NCSE patients and five TME patients in a pairwise manner, in all the 21 EEG channels. In each pair, the minimum length of the EEG recordings of the two compared patients is used for the comparison. The null hypothesis is that: two matched sample sets from any two patients, in the vectors X and Y, come from distribution with equal means. X − Y, the difference of X and Y, has vector elements assumed to come from a normal distribution with unknown variance. We performed the paired *t* test at a significance level 0.0001%, meaning the paired *t* test returns a 99.9999% confidence interval for the true mean of X − Y. We expect that the null hypothesis will be accepted for patients who belong to the same group and rejected for patients who belong to different groups.

The results of the *t* test (number of rejections of null hypothesis in each pair of patients, ranges from 0–21) are:

(1) For STLmax, the mean ± standard deviation
(a) pairs within NCSEs, (b) pairs between NCSE and TME, and (c) pairs within TMEs, are 5.8333 ± 6.1156, 20.2667 ± 1.7207, and 13.8400 ± 8.0347, respectively.

(2) For phase of attractor, the mean ± standard deviation
(a) pairs within NCSEs, (b) pairs between NCSE and TME, and (c) pairs within TMEs, are 10.6667 ± 6.2792, 19.7000 ± 1.8223, and 12.1600 ± 7.0810, respectively.

(3) For ApEn, the mean ± standard deviation
(a) pairs within NCSEs, (b) pairs between NCSE and TME, and (c) pairs within TMEs, are 10.8333 ± 7.3310, 8.3200 ± 6.0189, and 11.5667 ± 5.5441, respectively.

For STLmax and phase of attractor, the numbers of hypothesis rejections in pairs within the six NCSE patients are relatively small, whereas the numbers of hypothesis rejections in pairs between NCSE and TME are relatively larger. This is the reason why epochs of the six NCSE patients are grouped together and epochs of two different types of patients (NCSE and TME) are relatively scattered, as is shown in Figs. 2 and 3.

Furthermore, in pairs within the five TME patients, the numbers of null hypothesis rejections are larger than those in pairs within the six NCSE patients. This shows that the nonlinear dynamic measures of TME patients demonstrate larger variability compared to the dynamic measures of NCSE patients, which tend to be more similar. This implication is consistent with the results shown in Fig. 4.

There are two TME patients with EEG recordings of very short length. As mentioned previously, the minimum length of the EEG recordings of two patients is used for the comparison in the paired *t* test. However, when recording time is not of sufficient duration, epoch samples of

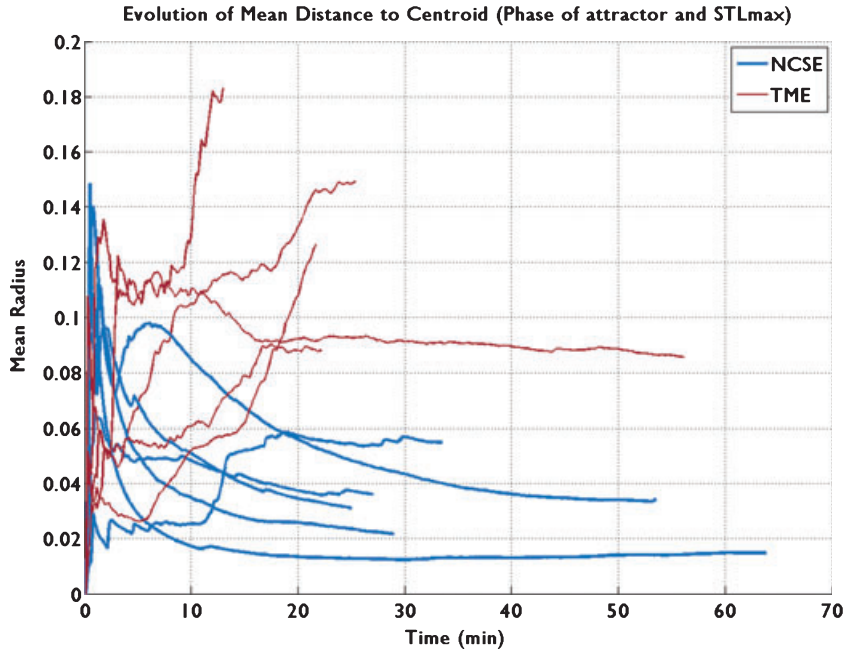

Figure 4.
Plot for the evolution of the mean radius to the centroid of points in two-dimensional feature space of STLmax and phase of attractor. Each curve is computed using full-length electroencephalography (EEG) recording of one patient. Mean radii of nonconvulsive status epilepticus (NCSE) patients (blue thick) after a time frame of 10∼20 min converge to some low values. On the other hand, mean radii of toxic/metabolic encephalopathy (TME) patients (red thin) tend to increase and do not converge fast.
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some NCSE patients may still be scattered in the multidimensional feature space of nonlinear dynamic measures, and may be close to epoch samples of the two TME patients. This gives an explanation why, in some EEG channels, the *t*-test in some pairs between NCSE and TME patients does not reject the null hypothesis. For approximate entropy (ApEn) the *t*-test indicates that there is no clear differentiation between generalized NCSE and TME.

Discussion

Distinguishing generalized equivocal EEG patterns (semi-rhythmic delta and triphasic-like waves) that can be seen in either NCSE or TME is a difficult clinical problem. Currently, the only effective method for distinguishing generalized NCSE from TME in equivocal cases is combining clinical judgment and experience (Bearden et al., 2008).

From the neuroscience perspective it would be interesting to uncover and model the basic mechanism that underlines the evolution of mental status changes of generalized NCSE patients, although at present the properties of epileptic brain are still not well understood. Nonlinear dynamics have been used in seizure detection and prediction in epilepsy over the last decade. The short-term Lyapunov exponent has been proposed as an indicative metric of the abrupt transient drop in chaoticity in EEG recording before seizure onset (Iasemidis et al., 1993, 1997, 2000, 2001, 2005). Another measure, approximate entropy (ApEn), which quantifies the unpredictability of fluctuations in a time series, has been proposed for EEG epileptic seizure detection (Srinivasan et al., 2007).

In this study, three nonlinear dynamic measures (STLmax, phase of attractor, and ApEn) were applied in order to distinguish between patients with generalized NCSE and patients with TME. Findings based on a dataset of 11 subjects suggest that two of those nonlinear dynamics, STLmax and phase of attractor, could potentially be used as a bedside assistive tool for diagnosis of generalized NCSE in intensive care units. These results may also provide additional evidence (through application other than seizure prediction or detection) that STLmax and phase of attractor can be useful in quantifying neurophysiologic states related to epilepsy. It is hoped that these results may trigger fruitful discussion among neurologists, clinicians, and scientists about the exact role of nonlinear dynamics in the field of epileptic disorders. Although groups of researchers relating epilepsy with dynamic systems (Milton & Jung, 2003) are active, at present there is no commonly accepted theory, and the mechanism of this connection remains unknown. Based on findings in this study, we suggest that epileptic activity is highly associated with dynamic system analysis.

As mentioned earlier, STLmax and phase of attractor were found most likely effective for differentiating generalized NCSE patients from TME patients. In the feature space spanned by STLmax and phase of attractor, for each patient, the mean distance from the centroid to all EEG samples is a useful metric to quantify the degree of concentration of EEG epochs. In the 11 subjects of our study, samples of any NCSE patient were more concentrated than samples of any TME patient. This indicates that the mean

distance can be utilized to assist in diagnosis of NCSE and implies a strong spatiotemporal synchronization of the brain dynamics.

The paired *t*-tests help quantify the efficacy of the three nonlinear dynamics (STLmax, phase of attractor, and ApEn) when differentiating NCSE from TME. Specifically, the paired *t*-test verifies that STLmax and phase of attractor could potentially be the base for an automatic machine learning classifier. Such a classifier would use dynamic support vector machine (D-SVM) or artificial neural network, and could be trained to do the classification of EEG recordings (Pardalos et al., 2004). For this purpose a larger training set is needed so that classification error can be minimized.

Although the small number of patients (11) used in this pilot study precludes us from reaching statistically significant conclusions, we are encouraged that two nonlinear dynamic measures (STLmax and phase of attractor) that we identified were able to accurately distinguish all of our patients across the two diseases. Moreover, these patients were selected because they had generalized EEG patterns that were particularly difficult to classify clinically. We anticipate a perspective study using a larger number of subjects to allow for further testing of the statistical significance of the results.

The proposed algorithm and measures may be used by the bedside during real-time EEG recording or off-line for postrecording analysis. The three nonlinear dynamic measures and derivative metrics proposed in this study were computed using a Dell XPS 1330 laptop computer (Intel Core-2 Duo T7500 CPU, 3G Memory). Finally it is noteworthy that, even with the above limited resources, the computations were accomplished almost in real-time, and therefore could have been implemented along with the recordings of the EEG, allowing for a rapid and accurate diagnosis of NCSE versus nonepileptic encephalopathy by the bedside.

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We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Mathematical description of the three nonlinear dynamical measures used in this study (**a**) Short term Lyapunov Exponents (STL-max) (**b**) Phase of Attractors (**c**) Approximate Entropy (ApEn).

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