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Time-Dependent Entropy Estimation of EEG Rhythm Changes Following Brain Ischemia

A. BEZERIANOS,[1,2] S. TONG,[1,3] and N. THAKOR[1]

[1]Department of Biomedical Engineering, School of Medicine, Johns Hopkins University, MD; [2]Department of Medical Physics, School of Medicine, University of Patras, Patras, Greece; and [3]Department of Biomedical Engineering, Shanghai Jiaotong University, Shanghai, China

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Abstract—Our approach is motivated by the need to generate a rigorous measure of the degree of disorder (or complexity) of the EEG signal in brain injury. Entropy is a method to quantify the order/disorder of a time series. It is the first time that a time-dependent entropy (TDE) is used in the quantification of brain injury level. The TDE was sensitive enough to monitor the significant changes in the subject's brain rhythms during recovery from global ischemic brain injury. Among the different entropy measures, we used Tsallis entropy. This entropy is parametrized and is able to match with the particular properties of EEG, like long-range rhythms, spikes, and bursts. The method was tested in a signal composed of segments of synthetic signals (Gaussian and uniform distributions) and segments of real signals. The real signal segments were extracted from normal EEG, EEG recordings from early recovery, and normal EEG corrupted by simulated spikes and bursts. Adult Wistar rats were subjected to asphyxia-cardiac arrest for 3 and 5 min. The TDE detected the pattern of ischemia-induced EEG alterations and was able to discriminate the different injury levels. Two parameters seem to be good descriptors of the recovery process; the mean entropy and the variance of the estimate followed opposite trends, with the mean entropy decreasing and its variance increasing with injury. *© 2003 Biomedical Engineering Society.* [DOI: 10.1114/1.1541013]

Keywords—Nonextensive, Electroencephalogram, Asphyxia, Rat.

INTRODUCTION

EEG is a sensitive but nonspecific measure of brain function and its use in cerebrovascular diseases is limited.[33] Nevertheless, it holds promise as a quantitative and real-time tool for diagnostic monitoring of brain injury. EEG has previously been used to prognosticate outcome after resuscitation from cardiac arrest (CA) with some success.[6,36] Our group has successfully utilized quantitative EEG measures to characterize the time and degree of electrophysiological response to CA.[14,32,40] The conventional approach to analyzing EEG rhythm is to obtain power spectra and delineate power in different spectral bands.[28,49] Alternatively, an algorithm that identifies dominant frequencies in EEG was shown to be more responsive to recovery patterns of brain rhythm following ischemic injury.[16] Clinically, it may be useful to obtain a single measure of such a recovery response as a diagnostic monitoring tool. Distance metrics, spectral and cepstral distance, have been proposed to determine the differences in the spectra of normal and injured brain.[15,25] However, such distance measures require comparison with base line, and in clinical situations, particularly unanticipated cardiac arrest, such base-line data are usually not available. Moreover, the distance metrics are not sensitive to the rapidly changing signal statistics (nonstationarities) of the recovering EEG.

The approach taken here is motivated by the need to develop a rigorous measure of the degree of disorder (or complexity) of the EEG signal in brain injury. The EEG signal complexity has been studied by means of the correlation dimension D_2.[10,27,41] A basic requirement for applying the tools of nonlinear dynamics (chaos theory) to experimental data is the stationary of the time series. This suggests that the time series is representative of a unique and stable attractor and is statistically invariant over different time intervals. Also, for the evaluation chaotic measures like D_2, long-time recordings are required. Generally, these measures are noise sensitive and their usefulness decreases especially in the case of additive noise.[4,5] Unfortunately, the EEG data are noisy and the stationarity requirement is not fulfilled; therefore, other methods have to be explored.

We postulate that entropy analysis will provide a quantitative measure of the degree of disorder in the brain rhythm at various times in brain injury and recovery. Approaches involving direct use of entropy for signal analysis have been reported.[7,26,31] Another method to measure complexity is to use the spectral entropy as defined from the Fourier power spectrum.[20,35] However, application of this method to short lasting and nonstationary data segments (such as EEG during recovery) has

Address correspondence to Nitish V. Thakor, Department of Biomedical Engineering, Johns Hopkins University, 720 Rutland Avenue, Baltimore, MD 21205-2195. Electronic mail: nthakor@bme.jhu.edu

the same limitations as previously described for the calculation of Fourier power spectra.

In the present paper we examine the question whether entropy can serve as a measure of transient or time-varying changes in the brain's recovery process after brain injury. In particular, we apply a time-dependent entropy (TDE) that is sensitive enough to monitor the significant changes in the subject's brain rhythms during recovery after global ischemic brain injury.

INFORMATION ENTROPY

Theoretical Background

In the development of the foundations of classical information theory, Khinchin[24] presented a mathematically rigorous proof of a uniqueness theorem for the Shannon entropy based on the additivity law for a composite system in terms of the concept of conditional entropy.

Suppose the total system can be divided into two subsystems, A and B, and let $p_{ij}(A,B)$ be the joint probability of finding A and B in their ith and jth microstates, respectively. Then, the conditional probability of B given that A is found in its ith state is given by $p_{ij}(B|A) = p_{ij}(A,B)/p_i(A)$, which leads to the celebrated Bayes multiplication law

$$p_{ij}(A,B) = p_i(A)p_{ij}(B|A), \tag{1}$$

where $p_i(A)$ is the marginal probability distribution: $p_i(A) = \Sigma_j p_{ij}(A,B)$. It should be noted that this form of factorization can always be established in any physical situation. The Shannon entropy[39] of the composite system is

$$S(A,B) = -k_B \sum_{i,j} p_{ij}(A,B) \ln p_{ij}(A,B). \tag{2}$$

Throughout the paper we use dimensionless units and the Boltzmann constant k_B is set equal to 1.

Thus, combining Eqs. (1) and (2) yields

$$S(A,B) = S(A) + S(B|A), \tag{3}$$

where $S(B|A)$ stands for the conditional entropy.[11]

In the particular case when A and B are statistically independent, $p_{ij}(B|A) = p_j(B)$ and from Eqs. (1) and (2) the additivity law $S(A,B) = S(A) + S(B)$ immediately follows. We emphasize here that there is a natural correspondence between the multiplication law and the additivity law:

$$p_{ij}(A,B) = p_i(A)p_{ij}(B|A) \Leftrightarrow S(A,B) = S(A) + S(B|A). \tag{4}$$

When the above discussion is generalized to any composite system there are theoretical and experimental considerations where systems do not obey the additivity law.[44] In this respect, a nonextensive generalization of Boltzmann–Gibbs statistical mechanics formulated by Tsallis[45] is better suited to describe such phenomena. In this formalism (often referred to as nonextensive statistical mechanics), Shannon entropy in Eq. (2) is generalized as follows:

$$S_q(A,B) = \frac{1}{1-q}\left\{ \sum_{i,j} [p_{ij}(A,B)]^q - 1 \right\}, \tag{5}$$

where q is a positive parameter. This quantity converges to the Shannon entropy in the limit $q \to 1$. Like the Shannon entropy, it is non-negative, possesses the definite concavity for all $q > 0$, and is known to satisfy the generalized H theorem. Nonextensive statistical mechanics has found a lot of physical applications. A standard discussion about the nonadditivity of the Tsallis entropy S_q assumes factorization of the joint probability distribution in Eq. (1) $[p_{ij}(A,B) = p_i(A)p_j(B)]$. Then, the Tsallis entropy is found to yield the so-called pseudoadditivity

$$S_q(A,B) = S_q(A) + S_q(B) + (1-q)S_q(A)S_q(B). \tag{6}$$

Clearly, the additivity holds if and only if $q \to 1$. However, there is a logical difficulty in this discussion. As mentioned above, Tsallis' nonextensivity was devised in order to treat a system with, for example, long-range interactions. On the other hand, physically ''dividing the total system into subsystems'' implies that the subsystems are spatially separated in such a way that there is no residual interaction or correlation. If the system is governed by a long-range interaction, the statistical independence can never be realized by any spatial separation since the influence of the interaction persists at all distances. In fact, the probability distribution in nonextensive statistical mechanics does not have a factorizable form even if systems A and B are dynamically independent, and therefore correlation is always induced by nonadditivity of statistics.[3]

Thus, it is clear that the assumption of the factorized joint probability distribution is not physically pertinent for characterizing the nonadditivity of the Tsallis entropy. These considerations naturally lead us to the necessity of defining a conditional entropy associated with the Tsallis entropy.

To overcome the above-mentioned logical difficulty and to generalize the correspondence relation in Eq. (4) simultaneously, Santos[38] proposed a generalization of Shannon's theorem to Tsallis entropy, Hotta and Joichi[19] investigated composability and generalized (Tsallis) en-

tropy, and Abe[2] extended the work of Santos[38] generalizing the Khinchin axioms for the ordinary information theory in a natural way to the nonextensive systems.

Along the lines of a recent paper of Abe and Rajagopal[1] the Tsallis entropy of the conditional probability distribution $p_{ij}(B|A)=p_{ij}(A,B)/p_i(A)$ is considered as

$$S_q(B|A)=\frac{S_q(A,B)-S_q(A)}{1+(1-q)S_q(A)}. \tag{7}$$

From this, we immediately see that

$$S_q(A,B)=S_q(A)+S_q(B|A)+(1-q)S_q(A)S_q(B|A), \tag{8}$$

which is a natural nonadditive generalization of Eq. (3) in view of pseudoadditivity in Eq. (6). Therefore, the correspondence relation in Eq. (4) now becomes

$$\begin{aligned} p_{ij}(A,B)=p_i(A)p_{ij}(B|A)&\Leftrightarrow S_q(A,B)\\ &=S_q(A)+S_q(B|A)+(1-q)S_q(A)S_q(B|A). \end{aligned} \tag{9}$$

Equation (9) coincides with Eq. (6) of pseudoadditivity when the two systems A and B are independent. In our application the A and B systems represent sources of brain activity at different times, which are especially distinguishable during brain recovery after ischemia[14,40] and the data analyzed are the weighed summation of source output traced in the temporal evolution of EEG recordings.

In this way the nonadditive Tsallis entropy was formulated according to the Khinchin axioms of information theory and the contradiction between dependency (Bayes law) and long range interaction (nonadditivity) is removed. Summarizing, we have established a rationale for a procedure for testing independence between random variables, which we propose as a practical tool to analyze the EEG recordings. The results depend upon entropic index q. It is expected that, for every specific use, better discrimination can be achieved with appropriate ranges of values q.

Signal Entropy

Shannon's entropy[39] has been accepted as a method to characterize information content in a signal. More recently it has been realized that the Shannon entropy fails to yield testable results for systems with long-range interactions, long-term memory effects, or abrupt changes.[43] This conforms with the observation that the evolution of EEG rhythm patterns, recorded during a specific physiological state, possess a multifractal statistical structure.[50] Therefore, it is reasonable to look for alternative information measures that may be better adapted to nonstationarity embedded in the time-varying nature of the distributions brought about by the multifractal nature of the rhythm generators.[41] To deal with such cases, we propose to use a nonlogarithmic form of entropy called Tsallis entropy.[45] This entropy is parametrized and it is possible to match it with the particular properties of EEG signals, like the long-range rhythms, bursts, and spikes. Tsallis entropy has been applied to the analysis of complex signals,[13,43] including the study of brain dynamics.[9,30] In these studies it was shown that the Tsallis information measure exhibits a surprising degree of sensitivity as a detector of changes in the parameters of brain dynamics, such as the presence of epileptic spikes.

Entropy is defined as a measure of uncertainty of information in a statistical description of a system.[11] In other words, the entropy is a measure of our ignorance about the system. The Shannon entropy [Eq. (2)], given a random variable X, where X takes discrete values x_i with probability p_i, is defined as

$$S=-\sum_{i=1}^{L} p_i \ln p_i, \tag{10}$$

where p_i is the probability that the signal belongs to a considered amplitude interval with L partitions and with the understanding that (a) $\Sigma_{i=1}^{L} p_i=1$ with $0\leqslant p_i\leqslant 1$, $i=1,\ldots,L$ and (b) $p_i \ln p_i=0$ if $p_i=0$. The Tsallis entropy [Eq. (5)] represents an extension of the original measure, and depends on a single additional real parameter $q>0$. For the same system as above its discrete version is

$$S_q=-(q-1)^{-1}\sum_{i=1}^{L}(p_i^q-p_i). \tag{11}$$

For $q\to 1$ Tsallis entropy coincides with Shannon entropy. Since the probabilities $\{p_i\}$ satisfy $p_i^q\geqslant p_i$ for $q<1$ and $p_i^q\leqslant p_i$ for $q>1$ (because for $\forall i p_i<1$), $q<1$ and $q>1$ will, respectively, emphasize the rare and the frequent events. For example, in the case of $q<1$ a rare event (the p_i^q term with $p_i\ll 1$) contributes much more in Tsallis entropy [Eq. (11)] than the same event (the p_i term with $p_i\ll 1$) in Shannon entropy [Eq. (10)]. The opposite happens in the case of $q>1$. It can also be shown that $S_q>=0$ and that S_q attains its maximum for $q>1$ for a uniform distribution (i.e., $p_i=1/L$), thus becoming $S_q=(q-1)^{-1}[1-L^{1-q}]$. On the other hand, for $0<q<1$, the S_q has a minimum at the same conditions as $q>1$ but is not upper bounded. In the next section we analyze EEG signals and calculate the Tsallis entropy for

$q>1$. It is expected that better discrimination of EEG signal features will be achieved with the appropriate selection of q values.

METHODS AND MATERIALS

Time-Dependent Entropy Estimation

In biomedical signal processing, data are usually modeled with a continuous probability density function (PDF). Usually what is considered, given a signal $s(t)$ and a time window $(0,T)$, is the entropy of the whole curve for the given temporal interval. In this case, there are two main approaches. First, the PDF can be approximated by an element of the parametrized set, whose entropy is known in term of the parameters.[11] Second, entropy estimators are based on *a priori* estimation of underlying PDFs by using kernel methods,[47] autoregressive (AR) modeling of PDF,[7] or histograms.[31] Such an entropy is not very helpful when the signal is not stationary and, in the case of EEG, nonstationarity results from a combination of spontaneous and burst activities. Instead, in such applications, what we need is a time-dependent entropy measure.

Let $s(t)$ denote the temporal evolution of the EEG signals. Consider the graph "signal amplitude $s(t)$ versus time" and a discrete-time set of amplitude values $D=\{s(t_k),k=1,2,\ldots,K\}$. For simplicity, from now on we use the notation $s(k)=s(t_k)$.

In order to compute the pertinent probability distribution, the amplitude domain D is partitioned into L equidistant boxes or disjoint amplitude intervals, I_l ($l=1,2,\ldots,L$) covering the space between maximum and minimum amplitude of the respective EEG segment. In particular, if

$$s_o=\min[D]=\min\{s(k),k=1,2,\ldots,K\},$$

$$s_L=\max[D]=\max\{s(k),k=1,2,\ldots,K\},$$

and

$$s_o<s_1<s_2\cdots<s_L,$$

then there is a set of boxes or disjoint intervals $\{I_l=[s_{l-1},s_l],l=1,2,\ldots,L\}$ such that

$$D=\overline{\bigcup_{l=1}^{L}} I_l.$$

We then define a sliding temporal window W depending on two parameters: the size w (an even number) and the sliding factor Δ. A sliding window of the data is defined according to

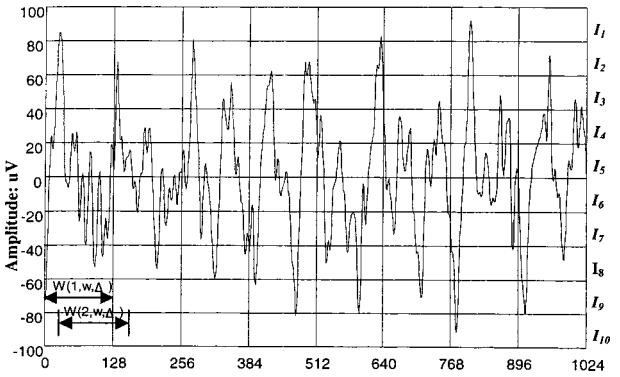

FIGURE 1. Time-dependent entropy estimation paradigm. The 1024 data points signal is partitioned to ten disjoint amplitude intervals. The window size is $w=128$ and it slides every $\Delta=32$ points.

$$W(m;w;\Delta)=\{s(k),k=1+m\Delta,\ldots,w+m\Delta\},$$

$$m=0,1,2,\ldots,M,$$

where Δ and w are selected such that $w\leqslant K$ $(K-w)/\Delta\in N$ and $M=(K-w)/\Delta$. The center of window W is $s(w/2+m\Delta)$ and m controls the consequential time displacement from the first $(m=0)$ to the last window $[m=(K-w)/\Delta)]$. Figure 1 is a time-dependent entropy estimation paradigm. The 1024 data points signal is partitioned into ten disjoint amplitude intervals. The window size is $w=128$ and it slides every $\Delta=32$ points.

The probability that the signal $s(k)\in W(m;w;\Delta)$ belongs to the interval I_l is denoted by $P^m(I_l)$. This probability is the ratio between the number of $s(k)$ values of $W(m;w;\Delta)$ found within I_l and the total number of $s(k)$ values in $W(m;w;\Delta)$.

The Shannon entropy measure associated with this probability is

$$SE(m)=-\sum_{l}^{L} P^m(I_l)\ln P^m(I_l), \tag{12}$$

while the corresponding Tsallis entropy measure is

$$TE(m)=-(q-1)^{-1}\sum_{l}^{L}[P^m(I_l)^q-P^m(I_l)]. \tag{13}$$

Subjects and EEG Recording

The experiments involved the study of neurological response to cardiac arrest resulting from various durations (typically, 3 or 5 min) of hypoxia and asphyxia followed by manual resuscitation and return of spontaneous circulation. Various durations of asphyxic cardiac arrest were induced and the rat were subsequently resuscitated by following a protocol modified by Katz and

colleagues.[23] Adult male Wistar rats ($300 \pm 25\,g$) were assigned to graded asphyxia of 3 min ($n=5$) and 5 min ($n=5$) that resulted in cardiac arrest. The mean duration of cardiopulmonary resuscitation (CPR) needed for successful resuscitation in the group of ten rats was 54.7 ± 12 s. A description of the animal model can be found in Geocadin *et al.*[15] The protocol was approved by the Animal Care and Use Committee of the Johns Hopkins Medical Institutions.

Two channels of EEG were recorded using subdermal needle electrodes (Grass Instruments, Quincy, MA) placed in the right and left parietal areas. Additionally, one channel of ECG and one channel of arterial pressure were recorded continuously before the insult, during the insult, and for 4 h after the insult. Data were saved on analog tapes by using ac preamplifiers (model 8-18D, Grass Instruments, Quincy, MA) coupled to a seven-channel FM tape data recorder (model MR-30, TEAC Corp., Japan). The amplifier cutoff frequencies were 0.3 and 70 Hz for the high and low passes, respectively. For the ECG recordings, the cutoff frequencies were set at 0.3–300 Hz. Power line noise was eliminated by using a 60 Hz notch filter. The EEG and the ECG signals were digitized simultaneously using the data acquisition package CODAS (DATAQ Instruments Inc., Akron, OH). Sampling frequencies of 250 Hz and 12 bit analog-to-digital (A/D) conversion were used for the EEG and ECG signals.

After preparation of the animal,[15] the base-line EEG was recorded for 15 min. This was followed by 5 min of asphyxic arrest. After the injury, CPR was carried out. The isoelectric pattern occurred initially, followed within 30 min by EEG with progressively increasing incidents of burst and burst suppression. Eventually, spontaneous EEG activity was restored after about 2 h.

In Fig. 2(A) a representative recording of a 4 h period experiment is plotted. In this recording we define the following periods: (I) (base-line or normal EEG), (II) (asphyxia), (III) (silent period or isoelectric), (IV) (early recovery), and (V) (late recovery). Segments of EEG, 10 s each, from these periods are shown in Fig. 2(B). The high amplitude signal at the beginning of period III [Fig. 2(A)] is an artifact due to CPR manipulations. During the silent period the EEG is strongly contaminated by an ECG artifact, which was removed before calculating entropy by the method of Tong *et al.*[42]

The Shannon and Tsallis entropies are calculated from Eqs. (12) and (13), respectively. There are no specific rules for selecting the values of the parameters w, Δ, and L. In the following we provide some information on the relation of these parameters to the time and frequency domain characteristics of the EEG and on the range of values of these parameters. The parameter Δ defines the resolution or the ''sampling period'' of the entropy when it is assessed as a dynamic phenomenon evolving in time. The lower value of Δ corresponds to the sampling frequency of the time series. The higher the entropy rate and the presence of spikes and bursts in the time series, the lower the sliding step used.

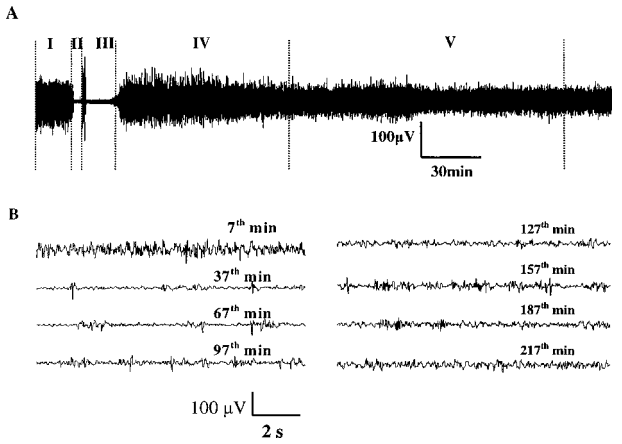

FIGURE 2. (A) 4 h EEG recording in a rat brain injury (asphyxic/cardiac arrest) experiment. Five regions (I–V) correspond to different phases of experiment. I: base line (20 min); II: asphyxia (5 min); III: silent phase after asphyxia (15 min); IV: early recovery (90 min); and V: late recovery (110 min). The high amplitude signal at the beginning of period III is an artifact due to cardiopulmonary resuscitation manipulations. (B) Detailed wave forms at the indicated time, 10 s each, from the above EEG recording.

The partition number L must be lower than the number of steps of the digitized amplitude, e.g., if the dynamic range is 8 bit then the amplitude is partitioned in $2^8=256$ equidistance intervals, and in this case $L<256$. The value selected for L is strongly related to the size of the window W and the PDF of the amplitudes of the segmented time series. Again, the rule is that the proper value of L, given the size w of window W, must give a ''smooth'' histogram.

Another problem, also related to the partition number L, is the error introduced by the finite window length w.[34] This leads to a bias of the entropy and unavoidable errors are introduced. Several methods have been proposed to remove this bias.[31,34,37] To investigate how the estimated entropy depends on the number w of data points (window size) we calculated the Shannon and Tsallis TDEs for a 1024 data-point segment of EEG.

We started with $w=64$ and increased up to the total signal duration $w=1024$ with step size 1. Our plots show that the entropy at $w=128$ is very close to the value of entropies with longer window size and the entropy does not increase dramatically by increasing the window size (Fig. 3). The choice of $w=128$ is close to the one used by others for TDE estimation.[8,9,30] Under these conditions direct calculation introduces a bias, with a relative value that is small in comparison to the mean value of TDE. Thus, in our case, as in other similar experiments[8,9,13,43] where local entropies (entropy of a

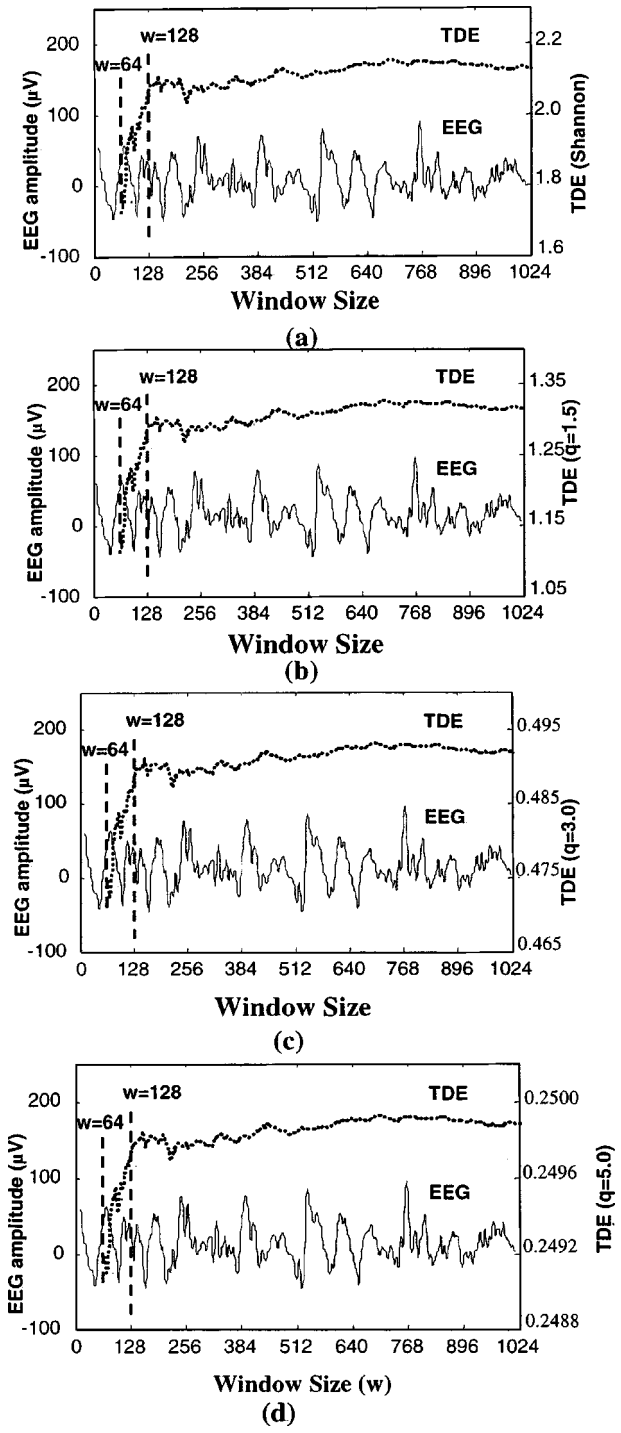

FIGURE 3. Effect of window size on time-dependent entropy. Four seconds of typical base-line EEG was chosen to calculate the time-dependent entropies with different q parameters. Panels (a)–(d) correspond to the Shannon entropy ($q=1.0$), Tsallis entropy ($q=1.5$), Tsallis entropy ($q=3.0$), and Tsallis entropy ($q=5.0$); we start from the window size $w=64$ to the total signal duration $w=1024$ and obtain the entropy vs. window size plots. The plots illustrate that the entropy at $w=128$ is very close to the stable value.

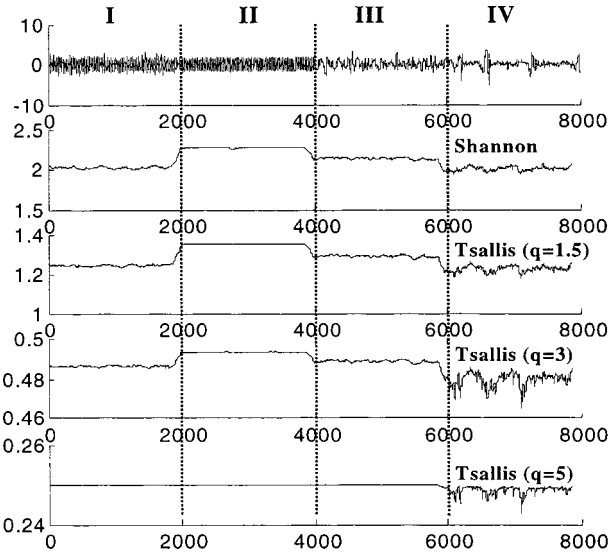

FIGURE 4. Composite signal (top) and Shannon and Tsallis entropy for different q index values ($q=1.5,3,5$). The signal is composed of four parts, 2000 data points each: Gaussian (I) and uniform (II) distributed noises, and segments of real signals from base-line (III) and early recovery EEG (IV). For $q=3$ the Tsallis entropy is sensitive enough to distinguish between signals with different probability distribution functions and to differentiate the base-line EEG from early recovery EEG.

signal within a short time window) were used, we did not need any bias correction in our entropy calculations.

For calculation of the TDE we selected (a) size window $w=128$ data points, (b) sliding step $\Delta=1$, and amplitude partition $L=10$. However, what makes the Tsallis entropy measure unique is the q parameter. The q parameter acts like a zoom lens for the data and can either focus on long-range rhythms (low values of q) or on short abrupt changes (bursts or spikes) (high values of q).[46] In our calculations we used $q=1.5$, 3, and 5.

RESULTS

Initially we explored the use of parametrized Tsallis entropy (function of q) to monitor the changes that the EEG undergoes during recovery and to compare it with the entropy of signals with known PDF. In particular, we compared the Tsallis and Shannon entropy measures on a composite signal (Fig. 4). It is composed by four parts, each with 2000 data points: a Gaussian (I) and a uniform (II) distributed noise as well as segments of real signals from base-line (III) and early recovery EEG (IV). Figure 4 (top to bottom) shows one realization of signal $s(t)$ and the mean value of Shannon and Tsallis entropies ($q=1.5$, 3, and 5) after 30 runs. Before calculation of the entropy, the various distributions are equated for variance.[12]

TABLE 1. Statistical analysis of Shannon and Tsallis entropy (q=1.5,3.0,5.0) of signals in Fig. 4: The values represent the mean value±standard deviation. [In parentheses the theoretical (exact) values.] The *t*-test was performed between (a) the parts of the signal with Gaussian and uniform distributions, and (b) base-line and early recovery EEG. SD=significant difference, degrees of freedom=58.

		Gaussian distribution	Uniform distribution	*t*-test	Base-line EEG	Early recovery EEG	*t*-test
Shannon		2.03±0.103 (1.926)	2.26±0.035 (2.30)	SD (1%) t=11.58	2.13±0.084	2.01±0.18	SD (1%) t=3.2
	q=1.5	1.24±0.059 (1.202)	1.35±0.017 (1.367)	SD (1%) t=9.82	1.29±0.07	1.22±0.118	SD (1%) t=2.95
Tsallis	q=3.0	0.483±0.004 (0.483)	0.494±0.00054 (0.495)	SD (1%) t=14.93	0.49±0.0076	0.48±0.014	SD (1%) t=3.40
	q=5.0	0.249±0.00015 (0.249)	0.2499±0.00036 (0.250)	SD (1%) t=12.64	0.25±0.00022	0.248±0.0018	SD (1%) t=6.04

Next, we examined if both Shannon and Tsallis entropy could be used to distinguish the various parts of the composite signal shown in Fig. 4. The mean value and the standard deviation of each part were calculated and *t*-tests were performed between the parts of signal: (a) Gaussian and uniform distributions; (b) base-line and recovery EEG. The results are summarized in Table 1, which includes the exact values of the entropies of Gaussian and uniform distributions.

The following points are important:

(1) The entropies, both Shannon and Tsallis, of the Gaussian noise are higher than their exact values, while the opposite is observed for the uniformly distributed noise. This is expected as the theoretical value of entropy for uniform distribution is the maximum entropy[11] and consequently the bias introduced, in our case, by the estimator used [Eqs. (12) and (13)], is negative (underestimation) while for the Gaussian noise a positive bias is introduced (overestimation).[7]
(2) The TDE (measured values) of the various parts of the signal is accurately estimated. We find: (a) the entropy is maximum for the uniform distribution and (b) the entropy of baseline EEG lies between the entropy of the two distributions (Fig. 4 and Table 1), which corresponds to the PDF shapes.
(3) Shannon and Tsallis TDE were shown to be robust enough to distinguish statistically the four different segments (Table 1).

Briefly, we have shown that both Shannon and Tsallis entropies can be used in their TDE fashion to monitor changes in the PDF of different class of signals.

In what follows, we will examine which of the two entropies can better detect the presence of spikes and bursts and, consequently, monitor the changes that the EEG undergoes during recovery from brain asphyxia, where the burst suppression EEG is dominant.[14,40] In this direction we explored the use of Tsallis entropy parametrized by the factor q to detect the presence of spikes and bursts in normal EEG,[9] and to compare its performance with the Shannon entropy.

We constructed a reference signal, combining a segment of spontaneous EEG and spikes as follows. A segment of 1 min EEG signal was extracted from normal activity (base line) before brain injury. The spikes appearing in EEG during recovery have the form of a biphasic wave with an attenuating tail and total length 0.22 s.[40] We simulated three cases of spikes with the same pattern of spike and amplitudes at 100%, 42%, and 8.3% (Fig. 5, top panel) of the initial spike.

Our results for Shannon and Tsallis entropy for q =1.5, 3, and 5 estimates are plotted in the lower panels of Fig. 5. It is clear that the parametrized Tsallis entropy with higher q values exhibits a better sensitivity than Shannon entropy for detecting the spikes (the higher the

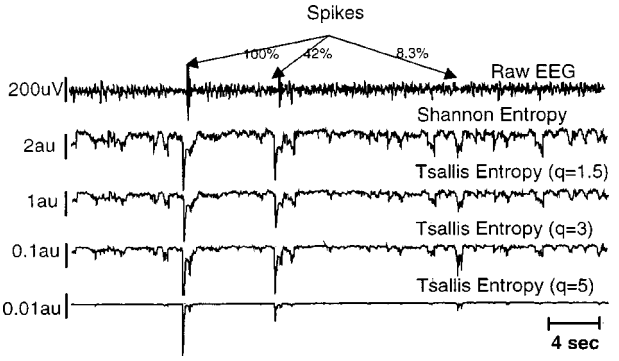

FIGURE 5. Simulation of EEG signal corrupted by three spikes (top). The three spikes, shown by arrows, are similar in shape but the amplitudes of the second and third spikes are 42% and 8.3% of the first spike amplitude. From top to bottom: the Shannon entropy and Tsallis ones for q=1.5, q =3, and q=5. Even with amplitude comparable to the EEG amplitude, the spikes are now detected and differentiated from the EEG signal for $q \geqslant 3$.

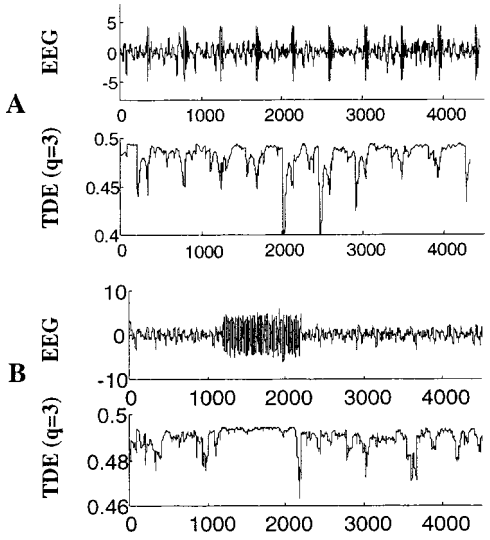

FIGURE 6. Same base-line EEG (segment III in Fig. 4) corrupted by spikes and a burst and their TE for $q=3$. (A) The spike duration is 0.22 s and the spike rhythm is 1 s^{-1}. (B) The rhythm of the 22 spike burst is 6 s^{-1}.

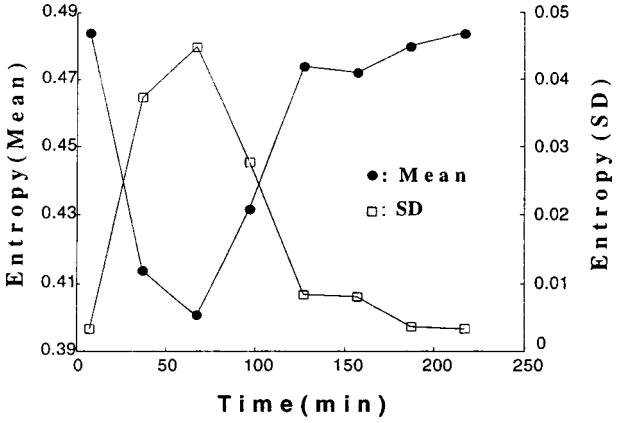

FIGURE 7. Mean Tsallis entropy ($q=3$) and the standard deviation of the entropy of 1 min EEG segments at the indicated times, from the 4 h EEG recording (Fig. 2) in a 5 min asphyxic/cardiac arrest experiment.

q, the better the detection). For example, in the vicinity of the second spike (amplitude 42%) the ratio spike amplitude/background variance is 4.4 in the Shannon case, while for $q=1.5$, 3.0, and 5.0 the Tsallis entropy it is 6.1, 12.6, and 33, respectively. Similar results were also found for the other spike amplitudes.

To compensate between the specificity to detect the bursts (locality) (it is better to use Tsallis entropy with high q) and the sensitivity to distinguish between different patterns of EEG (globality) (it is better to use either Shannon or Tsallis entropy with low q) (Fig. 4), we selected Tsallis entropy with $q=3$ for further analyses throughout the rest of the paper.

We then examined how much the Tsallis entropy of the EEG changes by the frequency of spikes and bursts (train of spikes). We simulated the cases where EEG is corrupted by spikes of frequency equal to 0.5 s^{-1} [Fig. 6(A)] and a burst of 22 spikes of 6 s^{-1} rhythm [Fig. 6(B)]. The spike duration corresponds to 22% of each cycle and the duration of the burst is 3.67 s. Figure 6 shows plots of the Tsallis entropy for $q=3$.

Then the mean value (MEAN) and the standard deviations (SDs) of the entropy across trials were calculated. The entropy (MEAN$\pm$SD) is 0.488 ± 0.004 (base line), 0.460 ± 0.020 (spikes), and 0.493 ± 0.001 (burst). These findings are in agreement with the results from the simulations. For example, the PDF of the burst itself is close to the uniform distribution (segment II in Fig. 4), which explains why its entropy is higher than the entropy of base-line EEG and of EEG corrupted by spikes. From these results we also see that entropy of the EEG decreases when EEG is corrupted by spikes, while the SD shows the opposite trend. We can explain this trend by looking at Fig. 5; every time a spike enters the moving window (within which the entropy is calculated), the entropy is decreased drastically. Thus, the entropy of base-line EEG is always higher than the entropy of intervening spikes. With respect to the MEAN of the EEG, it becomes high when the spontaneous activity is prominent and low when spikes are present. Also, the SD of the signal is related to the spikes and their frequency. Increasing the frequency of the spikes causes an increase in SD because the number of spikes goes up (results not shown).

Next, we analyzed EEG segments, 1 min each, extracted from the 4 h continuous recording of an ischemic insult experiment with 5 min asphyxia. One segment of base line, one silent period, three early recovery segments, and three late recovery EEG segments were analyzed. Figure 2(B) shows segments of 10 s each from those analyzed. The TDE was calculated with parameters $w=128$, $\Delta=1$, $L=10$, and $q=3$. The mean value and the standard deviation of Tsallis entropy were calculated and plotted for all segments (Fig. 7). The plots correspond to the characteristic electrophysiological patterns of the EEG during the experiment [Fig. 2(A)]. The MEAN reflects mainly the changes in EEG spontaneous activity, while the SD reflects the spike activity. The results are in agreement with the calculations of Tsallis entropy from the composite signals (Figs. 4 and 6).

Finally, we monitored the overall recovery profile after an ischemic insult. The experiments were designed to study the influence of duration of asphyxia on brain recovery. We present results from two groups of animals with asphyxia times of 3 min ($n=5$) and 5 min ($n=5$). The grand average entropy mean value and variance are plotted in Fig. 8. The sharp drop/rise in MEAN/variance corresponds to the injury incident followed by

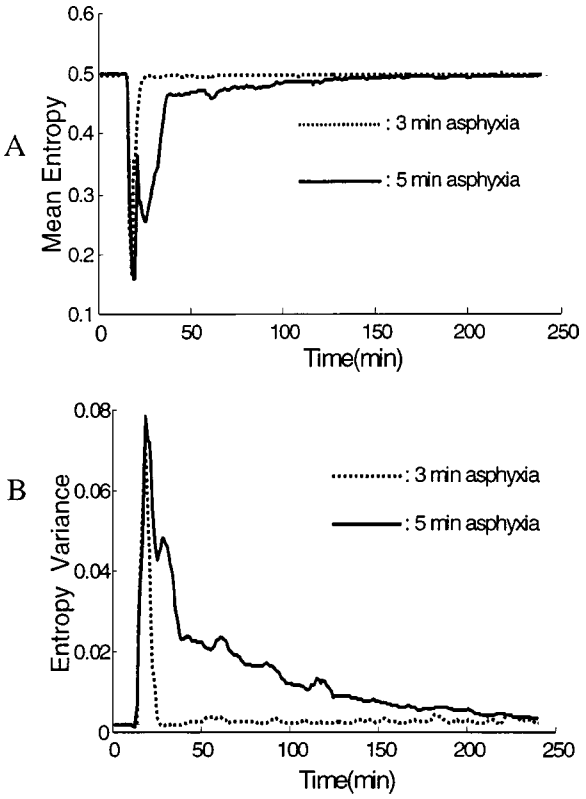

FIGURE 8. Grand average entropy trends for the EEG from animal subjects from 3 and 5 min asphyxia. Mean entropy (A) and variance of entropy (B) are plotted over ~4 h continuously. The sharp drop/rise corresponds to the injury incident, followed by progressive recovery indicating partial restoration of brain functioning.

recovery over the next 4 h, indicating restoration of normal EEG. In both groups of animals the mean entropy returns to its value before the asphyxia [Fig. 8(A)] faster than the variance [Fig. 8(B)]. This may indicate that during recovery the spontaneous activity returns to the normal earlier than the cessation of spike activity. These findings are in agreement with the results from previous work on cepstral distance[15] and suppression EEG (Ref. 40) of brain after recovery from asphyxia. The characteristic differences between the two groups are: (a) in earlier stages, the entropy recovery rate is higher in the group of animals with 3 min asphyxia and reaches a plateau sooner, and (b) in the late stages of recovery the entropy stabilizes and presents a plateau for both groups, earlier for mean and later for variance. Thus, the rate (time derivative) with which the entropy comes back to normal can be used as a parameter to characterize the degree of injury.

Furthermore, from each TDE trace, segments of 10 min (3 min from the asphyxia period) were selected, the corresponding time average values were calculated, and the statistical table for each animal group was constructed. The mean TDE is differentiated (level of confidence 1%) among the two groups (3 min vs. 5 min) (Table 1) only within the early recovery period, while the variance is significantly different among all the segments analyzed (Tables 2 and 3). Because of the small animal population, we cannot be sure which of the two parameters is better and further study with a larger population is needed.

DISCUSSION

The EEG has been used as an indicator of cerebral metabolism[21] and is profoundly affected by transient ischemia. The pattern of ischemia-induced EEG alterations is stereotypic and common to humans, primates, rats, and other mammals,[18,29,48] In all animal experiments where brain injury is studied, the EEG subsides to an isoelectric pattern within the first 2 min of asphyxia. After resuscitation, EEG recovery is punctuated by periods of electrical silence and bursts in energy, commonly known as burst suppression or simply bursting. EEG activity progressively increases in amplitude and is enriched in frequencies. These changes are manifested in the recovering EEG in a global sense and last for 3–4 h after resuscitation when the physiological state of the animal is stabilized and the EEG signal becomes almost stationary for small time windows (3–5 s).

The conventional approach to analyzing EEG rhythm would be to obtain power spectra and delineate power in different spectral bands.[28,49] Our previous work showed

TABLE 2. Statistical analysis of mean of the EEG grand average TDE, from animal subjects in 3 and 5 min asphyxia, calculated for a time span of 10 min, except asphyxia where the mean value was calculated within 3 min. NS=not significant; SD=significant difference, degrees of freedom=8.

	Base line 1st–10th min	Asphyxia 15th–18th min	Early recovery 60th–70th min	Recovery 90th–100th min	Recovery 160th–170th min
3 min	0.4974±0.000714	0.35±0.1	0.4951±0.00065	0.4957±0.00044	0.4960±0.0012
5 min	0.4980±0.00080	0.34±0.1	0.4833±0.000433	0.4890±0.0008	0.4950±0.00024
t-test	NS (1%) $t=1.1142$	NS (1%) $t=0.2080$	SD (1%) $t=33.8$	SD (1%) $t=16.4$	NS (1%) $t=2.0099$

TABLE 3. Statistical analysis of variance of the EEG grand average TDE, from animal subjects in 3 and 5 min asphyxia, calculated for a time span of 10 min, except asphyxia where the variance was calculated within 3 min. NS=not significant; SD=significant difference, degrees of freedom=8.

	Base line 1st–10th min	Asphyxia 15th–18th min	Early recovery 60th–70th min	Recovery 90th–100th min	Recovery 160th–170th min
3 min	0.0020±0.00019	0.07±0.0082	0.0035±0.000627	0.0019±0.000597	0.0033±0.0016
5 min	0.0025±0.00014	0.065±0.0093	0.026±0.0035	0.022±0.0056	0.0075±0.0004
t-test	SD (1%) $t=4.7373$	NS (1%) $t=0.9017$	SD (1%) $t=14.1495$	SD (1%) $t=7.9807$	SD (1%) $t=6.5079$

that distance metrics (spectral and cepstral distance) for characterizing the injury and recovering EEG were far more sensitive to the detection of injury than the signal power itself.[15,25] However, the distance measures (spectral or cepstral) are not specific enough to track the recovery profile of EEG. Comparison with base-line power is needed, which is usually not available.

The concept of Shannon entropy has played a significant role in a variety of scientific and engineering areas. Its original meaning connotes uncertainty of information such as disorder, equality (discrepancy), diversity, and so on.[17] Unlike the computation of signal power, entropy measures are independent of the instrumental amplitude changes. This is because the entropy is invariant if a constant is added to the signal and if this same signal is multiplied by a constant different from zero. Also, the entropy estimated for the current window is tightly linked to the measurements obtained from a fixed number of the past time windows. Interesting approaches involving direct use of entropy for signal analysis can be found in Refs. 7, 26, and 31. In these reports a measure of complexity of the underlying probability density functions allows the design of an optimal processing scheme to solve different problems like source coding, image alignment, and detection of abrupt changes. We extended our previous study to early detection and measurement of cerebral ischemia with metrics like Itakura and cepstral distances.[15,25] These metrics are limited by the necessity for a base-line measurement of EEG and modeling of EEG as an AR stochastic process. Moreover, in these studies either short EEG recordings were used[25] or arbitrary indices and thresholds were introduced.[25] We used a TDE which is not limited by either nonstationarity or nonlinearities of the EEG or the length of the data needed for efficient and statistically accepted calculations. Concerning the Renyi entropy[22] although parametric, we did not use it as we considered it as an additive entropy (logarithmic entropy) like the Shannon entropy.[43,45] Up to now Tsallis entropy has been described as a tool to detect epileptic spikes[9,30] and it is the first time that it is used in the quantification of brain injury levels. We found out that Tsallis entropy can discriminate the different injury levels and different segments of recovery. Also, in this work the role of the q parameter was tested experimentally in simulations and real EEG signals. Excluding the silent period where the signal is dominated by heart activity[42] and no further discussion is able to be done, the period where burst and burst–suppression patterns occurs (early recovery period) can be easily differentiated from base line with both derived parameters. The mean value and the variance of Tsallis TDE are lower/higher, respectively, of the base-line ones. But, what can be used for monitoring the recovery after asphyxia is the rate (time derivative) of these parameters, which seems to be even more sensitive to the experiment conditions, e.g., asphyxia duration (Fig. 8). Our method should also be useful, when properly modified (e.g., using higher q values), for detecting the spike activity or bursts encountered during long-term observations ($t>4$ h) in critical care settings. Two parameters seem to be good descriptors of the recovery process: the time derivative of the entropy during early recovery; and the difference in entropy as compared with the base-line entropy. Although the base-line comparison can only occasionally be used clinically, the rate (time derivative) of entropy is an independent measure that can be used for prognostication of recovery.

CONCLUSION

Information measures, like Shannon and Tsallis entropies, describe satisfactorily the complexity of the EEG and the changes that occur after an ischemic insult. In this work, we have analyzed four EEG recordings and observed statistically significant differences between base-line EEG and EEG after asphyxia up to the initial phase of late recovery ($t\sim2$ h) This is a significant increase over the observation window of a previous work where the spectral distance was calculated.[10] Moreover, our method can be used to monitor the EEG changes after asphyxia without the necessity of base-line EEG.[15]

Therefore, the asphyxia period (silent period) as well as the early recovery (burst–suppression EEG) are discriminated from the base-line EEG. The main new feature in our work is that entropy measures are able to

detect quantitatively changes produced by variations of the experimental settings (like asphyxia duration).

Thus, a future challenge in this direction is to use time-dependent entropy graphs in order to extract new parameters to characterize electrophysiologic responses encountered after brain injury in an objective manner. The animal studies we have presented set the stage for utilizing entropy-based methods to characterize brain rhythms in humans in critical care settings.

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