Journal of Theoretical Biology 289 (2011) 160–166

Contents lists available at SciVerse ScienceDirect

Journal of Theoretical Biology

journal homepage: www.elsevier.com/locate/yjtbi

Surrogate data modeling the relationship between high frequency amplitudes and Higuchi fractal dimension of EEG signals in anesthetized rats

Sladjana Spasic [a,*], Aleksandar Kalauzi [a], Srdjan Kesic [b], Milica Obradovic [c], Jasna Saponjic [b,**]

[a] University of Belgrade, Department for Life Sciences, Institute for Multidisciplinary Research, Kneza Viseslava 1, 11 030 Belgrade, Serbia
[b] University of Belgrade, Department of Neurobiology, Institute for Biological Research—Sinisa Stankovic, Despot Stefan Blvd. 142, 11060 Belgrade, Serbia
[c] University of Belgrade, Medical School, Department of Pulmonary Medicine, Clinical Center "Bezanijska Kosa", 11 000 Belgrade, Serbia

ARTICLE INFO

Article history:
Received 24 February 2011
Received in revised form
25 August 2011
Accepted 29 August 2011
Available online 5 September 2011

Keywords:
Higuchi fractal dimension
Spectral–fractal relationship
Ketamine/xylazine
Nembutal
Anesthesia

ABSTRACT

We used spectral analysis and Higuchi fractal dimension (FD) to correlate the EEG spectral characteristics of the sensorimotor cortex, hippocampus, and pons with their corresponding EEG signal complexities in anesthetized rats. We have explored the quantitative relationship between the mean FDs and EEG wide range high frequency (8–50 Hz) activity during ketamine/xylazine versus nembutal anesthesia at surgical plane.

Using FD we detected distinct inter-structure complexity pattern and uncovered for the first time that the polygraphically and behaviorally defined anesthetized state at surgical plane as equal during experiment in two anesthetic regimens, is not the same with respect to the degree of neuronal activity (degree of generalized neuronal inhibition achieved) at different brain levels.

Using the correlation of certain brain structure EEG spectral characteristics with their corresponding FDs, and the surrogate data modeling, we determined what particular frequency band contributes to EEG complexities in ketamine/xylazine versus nembutal anesthesia.

In this study we have shown that the quantitative relationship between higher frequency EEG amplitude and EEG complexity is the best-modeled by surrogate data as a 3rd order polynomial.

On the base of our EEG amplitude/EEG complexity relationship model, and the evidenced spectral differences in ketamine versus nembutal anesthesia we have proved that higher amplitudes of sigma, beta, and gamma frequency in ketamine anesthesia yields to higher FDs.

1. Introduction

The Lempel–Ziv complexity, Shannon end approximate entropy, Higuchi fractal dimension (FD), correlation dimension, and other nonlinear measures of the electroencephalogram (EEG) have been recently proposed as the measures of sedation, and anesthesia depth (Widman et al., 2000; Bruhn et al., 2000; Zhang et al., 2001; Anier et al., 2004; Van den Broek et al., 2000; Ferenets et al., 2006; Ferenets et al., 2006; Klonowski et al., 2006).

In our former study (Spasic et al., 2011) we hypothesized that at appropriately achieved surgical plane of anesthesia, behaviorally and polygraphically controlled and defined as the same brain state, it is possible to detect different complexity of the EEG signals within the distinct brain structures, as the consequence of the different mechanisms of anesthetic action (ketamine/xylazine versus nembutal anesthetic regimen). We have evidenced for the first time that different anesthetic regimen determines the brain inter-structure EEG complexity pattern, and proved FD as a valuable tool for measuring the anesthesia induced inter-structure EEG complexity and for detection of different state of the brain during the same behavior.

Mathematical exactness could not be easily translated to biomedical research, and the limitations of various tools, particularly fractal analysis, could be critically evaluated (Eke et al., 2002). The criticism of the use of FD in identifying different physiological states might be linked to the corresponding considerable data reduction—from a vector of complex numbers of spectral values to one real scalar (FD). Consequently, complexity of a signal is determined by the corresponding FFT spectral profile, while solution of the inverse problem is not unique, i.e. a particular Higuchi FD may be attributed to signals of different spectra. This and the other similar circumstances are probably the cause why a detailed and accurate quantitative link between these two quantities is still missing, and only a few papers addressed this issue (Ziller et al., 1995; Navascués and Sebastián 2006).

In this study we used spectral analysis and FD to correlate the EEG spectral characteristics of the sensorimotor cortex, hippocampus, and

* Corresponding author. Tel.: +381 11 2078465; fax: +381 11 2761433.
** Corresponding author.
E-mail addresses: sladjana@imsi.rs, sladjana@ibiss.bg.ac.rs (S. Spasic), jasnasap@ibiss.bg.ac.rs, jasnasaponjic@yahoo.com (J. Saponjic).

0022-5193/$ - see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.jtbi.2011.08.037

pons with their corresponding EEG signal complexities in anesthetized rats, and we have explored the quantitative relationship between the mean FDs and EEG wide range high frequency (8–50 Hz) activities during stable ketamine/xylazine versus nembutal anesthesia at surgical plane. Using the correlation of certain brain structure EEG spectral characteristics with their corresponding FDs, and the surrogate data modeling, we determined what particular of the five tested frequency bands contributes to EEG signal complexities in ketamine/xylazine versus nembutal anesthesia.

2. Materials and methods

2.1. Experimental procedure and data

Experiments were performed in 17 male Sprague Dawley rats, weighing 200–300 g prior to surgery, maintained on a 12 h light-dark cycle, and housed at 25 °C with free access to food and water. Principles for the care and use of laboratory animals in research were strictly followed, as outlined by the Guide for the Care and use of Laboratory Animals (National Academy of Sciences Press, Washington, DC, 1996).

Rats were anesthetized with a combination of 80 mg/kg ketamine (Abbott Laboratories, North Chicago, IL), and 5 mg/kg xylazine (Phoenix Scientific Inc. St Joseph, MO) (8/17) or with 50 mg/kg nembutal (9/17) given by intraperitoneal injection. After a surgical plane of anesthesia was achieved (controlled by absence of the tail- or ear-pinch and corneal reflexes), rats were placed in the stereotaxic apparatus (David Kopf Inst., model 962 A Tujunga, CA). Following the electrodes implantation, bilateral referential EEGs were recorded using stainless screws in the parietal cortex (P: 2.5; R/L: 2; V: 1 to bregma), and teflon coated wires (Medwire, MT. Vernon, NY) in the CA1 region of hippocampus (P: 3.8; R/L: 1.7; V: 2.7 to bregma). A bipolar twisted wire electrode with uninsulated tips of 1 mm was stereotaxically targeted into right pedunculopontine tegmental nucleus (PPT) to record the pontine EEG (P: 8; R: 1.8; V: 7 to bregma).

During each experimental protocol, we performed an 8-channel recording: (1) respiratory movements monitored by a piezoelectric strain gauge (Infant-Ped Sleepmate Technologies, Mislothian, VA); (2) an injection marker signal obtained from MPPI-2; (3) EEG from left sensorimotor cortex; (4) EEG from right sensorimotor cortex; (5) left hippocampal EEG; (6) right hippocampal EEG; (7) right pontine EEG; (8) genioglossal EMG. The details of this method are more fully explained elsewhere (Saponjic et al., 2005; Saponjic et al., 2006). After conventional amplification and filtering (0.1–50 Hz band-pass; Grass Model 12, West Warwick) the analog data were digitized (sampling frequency 100/s) and recorded using Brain Wave for Windows software (Datawave Systems, Longmont, CO).

In this study we used 180 s of all EEG records during stable control anesthetized condition at surgical plane of anesthesia: (1) EEG from left sensorimotor cortex (Cx left); (2) EEG from right sensorimotor cortex (Cx right); (3) left hippocampal EEG (Hipp left); (4) right hippocampal EEG (Hipp right); (5) right pontine EEG (pons).

2.2. Fractal analysis

Fractal analysis was performed by estimating the Higuchi fractal dimensions (FDs) (Higuchi, 1988) of EEG signals from the certain brain structures in both anesthetic regimens. Fractal dimension is a nonlinear measure of signal complexity in time domain. EEG was analyzed in time sequences $x(1)$, $x(2)$, …, $x(N)$, and it was constructed in a new self-similar time series X_k^m as

$$X_k^m : x(m), x(m+k), x(m+2k), \ldots, x(m+\mathrm{int}[(N-k)/k]k)$$

for $m=1, 2, \ldots, k$ where m is initial time; $k=2, \ldots, k_{\max}$, where k is time interval; $k_{\max}$ is a free parameter; int(r) is integer part of the real number r. The length $L_m(k)$ was computed for each of the k time series or curves X_k^m.

$$L_m(k) = \frac{1}{k}\left[\left(\sum_{i=1}^{\mathrm{int}[(N-m)/k]} |x(m+ik) - x(m+(i-1)k)|\right)\frac{N-1}{\mathrm{int}[(N-m)/k]}\right]$$

where N is the length of the original time series X and $(N-1)/\{\mathrm{int}[(N-m)/k]k\}$ is a normalization factor. $L_m(k)$ was averaged for all m forming the mean value of the curve length $L(k)$ for each $k=2, \ldots, k_{\max}$ as

$$L(k) = \frac{\sum_{m=1}^{k} Lm(k)}{k}$$

An array of mean values $L(k)$ was obtained and the FD was estimated as the slope of least squares linear best fit from the plot of $\ln(L(k))$ versus $\ln(1/k)$

$$\mathrm{FD} = \ln(L(k))/\ln(1/k)$$

After preliminary tests, our results confirm that the FD is independent of the length of the window, at least for $N > 100$, but much more dependent of the parameter $k_{\max}$. So, we chose the parameter $N=500$ equivalent to an epoch of 5 s duration, and the parameter $k_{\max}=8$. We used the parameter $k_{\max}=8$ on the basis of our former study of the optimum choice for $k_{\max}$ value (Spasic et al., 2005).

EEG signals were divided into 36 epochs (windows). FD values were calculated for each epoch, without overlap. Individual FD values were averaged across all epochs for the signal. Higuchi's algorithm is applied using MATLAB software that has been validated in our previous publications (Spasic et al., 2011; Spasic et al., 2005; Spasic et al., 2008; Kalauzi et al., 2005).

In order to facilitate an interpretation of the EEG signals FD values, the FD value of smooth curve (for example linear or a low frequency sine wave) was estimated to be ~1. The FD of random white noise was estimated to be ~2.

2.3. Spectral analysis

We calculated Fourier amplitude spectra on each 5 s epoch during overall 180 s of stable control anesthetized condition for each animal, and for all 5 recorded structures as described before. For each type of anesthesia, and each recorded structure we averaged normalized amplitude spectra (for nembutal anesthesia $n=9$; for ketamine/xylazine anesthesia $n=8$), and calculated relative amplitude spectra. We analyzed the amplitude changes induced by ketamine/xylazine or nembutal anesthesia of all conventional frequency bands excluding alpha, which is not well expressed in rats ($\delta=0.2$–4 Hz; $\theta=4.2$–8 Hz; $\sigma=8.2$–14 Hz; $\beta=14.2$–30 Hz; $\gamma=30.2$–50 Hz).

2.4. Surrogate data generation

Before any analysis of the biological signals using some nonlinear method, such as fractal analysis, it is very important to test the presence of nonlinearity within original data (Spasic et al., 2011; Schreiber and Schmitz, 2000; Spasić, 2010). In our previous works (Spasic et al., 2011; Spasić, 2010), the surrogate data tests served to resolve if there are any residues of deterministic or nonlinear processes, that can be traced in biological signal, and to formulate this problem as a hypothesis testing. The null hypothesis H_0 was that the signal is generated by a statically transformed autoregressive process (Kugiumtzis, 2002). In order to reject or approve this null hypothesis, the surrogate data, generated to represent the null hypothesis, are compared to the original data