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Visualization and Modelling of STLmax Topographic Brain

Activity Maps

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Abstract

This paper evaluates the descriptive power of brain topography based on a dynamical parameter, the Short-Term Maximum Lyapunov Exponent (STLmax), estimated from EEG, for finding out a relationship of STLmax spatial distribution with the onset zone and with the mechanisms leading to epileptic seizures. Our preliminary work showed that visual assessment of STLmax topography exhibited a link with the location of seizure onset zone. The objective of the present work is to model the spatial distribution of STLmax in order to automatically extract these features from the maps. One-hour preictal segments from four long-term continuous EEG recordings (two scalp and two intracranial) were processed and the corresponding STLmax profiles were estimated. The spatial STLmax maps were modelled by a combination of two Gaussians functions. The parameters of the fitted model allow automatic extraction of quantitative information about the spatial distribution of STLmax: the EEG signal recorded from the brain region where seizures originate exhibited low-STLmax levels, long before the seizure onset, in 3 out of 4 patients (1 out of 2 of scalp patients and 2 out of 2 in intracranial patients). Topographic maps extracted directly from the EEG power did not provide useful information about the location, therefore we conclude that the analysis so far carried out suggests the possibility of using a model of STLmax topography as a tool for monitoring the evolution of epileptic brain dynamics. In the future, a more elaborate approach will be investigated in order to improve the specificity of the method.

Keywords

Electroencephalography; STLmax; Brain Mapping; Gaussian Modelling

1. Introduction

Electroencephalographic (EEG) brain topography was born at the end of the 80s. It is a neuroimaging technique that consists of plotting over the head color coded contours of brain activity features, most commonly the frequency and/or the power. This approach gives a spatial

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view of frequency or/and amplitude of EEG modulations co-registered to the scalp location. Topographic analysis may help clinicians reach diagnostics [Harner 1986, Nuwer 1988, Babiloni et al. 2004], because it easily pinpoints the exact location of EEG alterations. In particular, EEG topography has been used as a tool for investigating the activity of epileptic brains during the ictal stage for onset zone localization [Miyagi et al. 2005, Ebersole 1997, Schreg 1994, Tekgul et al. 2005, Nayak et al. 2004, Skrandies and Dralle 2004, Clemens 2002, Tsai et al. 2001, Crone et al. 2001]. Moreover, finding parameters with a topographic significance has been intensively addressed in scalp potential topography and EEG frequency analysis [Samson-Dollfus D. et al. 1987, Harner R.N. et al. 1987, Kowada M. et al. 1989, Nuwer M.R. 1988, Zoly J. Koles and R. B. Paranjape 1988]. However, to our best knowledge, topographic displays of nonlinear EEG descriptors have not been proposed nor clinically validated. This is long overdue because the information is easily assimilated by the clinicians and can serve as a preliminary evaluation of the methods, although a quantitative analysis will still be necessary. Modelling the topography of the Short-Term Maximum Lyapunov Exponent (STLmax) activity in each frame of the movies constitutes an intermediate level of quantification when compared with full analytical description of the spatial temporal multichannel signal, and will be the method developed in this paper.

The concept of epilepsy as a dynamical disease, a term introduced by Mackey and Glass in 1977 (Mackey and Glass, 1977; Mackey and an der Heiden, 1982) motivated the study of EEG dynamics. Many researchers (Milton [Milton J. and Black D. 1995], Lopes da Silva [Van der Heyden et al. 1999], Sackellares [Sackellares et al. 2000]) modelled epilepsy as a brain dynamical disease, because complex nonlinear dynamics can explain how biological systems make fast transitions between normal and pathological states. It was hypothesized that pathological states, such as an epileptic seizure, could result from transitions between higher dimensional to lower dimensional attractor states [Iasemidis et al., 1990, Iasemidis and Sackellares, 1996, Sackellares et al. 2000]. Irrespective of this hypothesis (see Mormann et al. 2007, Theiler et al., 1992; Palus, 1996 for dissenting opinions), the assumption of an underlying nonlinear dynamical system for EEG generation is less restrictive than the commonly used linear modelling approach (a linear system excited by white noise).

Therefore, since EEG signals translate brain functions spatially and temporally, dynamical EEG descriptors of chaotic dynamical system states such as the Teager Energy [Milton J. and Black D. 1995], correlation dimension [Van der Heyden et al. 1999] or Lyapunov exponents can potentially provide clinically useful quantification of the brain state [Iasemidis et al. 1994]. Previous work has shown that the STLmax starts dropping at critical electrode sites during the preictal stage, continuing to drop until the brain enters the ictal stage, and increases again in the postictal stage [Sackellares 2006]. This is consistent with the hypothesis that the epileptic brain transits from a low-order dynamical condition to a higher-order condition when a seizure is approaching, because of abnormal synchronization of the bio-electric fields generated by groups of neurons. Since our group has investigated STLmax for over a decade to quantify the epileptic brain dynamics [Sackellares et al. 2006], it seems very appropriate to investigate brain topography using Lyapunov exponents [Mammone et al. 2006].

Lyapunov exponents are directly related to the real value of the eigenvalues of the linearized system [Iasemidis et al. 1990] and hence they are related to the local stability of the underlying system. The appeal of the STLmax is that it can be reasonably well estimated directly from data [Wolf et al. 1985] without performing a full eigen-decomposition of the dynamics in the tangent space. Therefore, the value of the STLmax quantifies the power of the projection in the direction of maximum rate of change. If the generating model was linear, this would basically correspond to the power of the signal along the principal eigen-direction. Thus, for nonlinear systems, the STLmax describes the system dynamics more accurately and it seems a plausible alternative to EEG power in the creation of topographic maps.

A recent paper by the authors described a brain mapping tool for long term monitoring of patients affected by intractable epilepsy based on the STLmax topography [Mammone et al. 2006]. Movies of STLmax topography evolution over many hours were created and visually reviewed. The paper showed that visual analysis of the STLmax brain mapping movies was more telling about the seizure zone, epileptic seizure segments and interictal activity than the conventional EEG power brain mapping. STLmax topographic mapping has allowed the authors to follow the spatial changes in brain dynamics over time, in particular, it showed relationship between the epileptogenic onset zone and low-STLmax levels, as well as between the areas with inter-ictal epileptiform activity and high-STLmax levels (Mammone et al. 2006). This approach gave a helpful and representative view of alterations of STLmax. The topographic map constructed with EEG power (standard EEG topography) showed much weaker spatial relationships with the epileptic activity even when patients were monitored through intracranial EEG.

One limitation of the previous study was that these assessments were obtained solely by visually reviewing the STLmax topographic map movies, and thus their interpretation was subjective. Moreover, in long-term EEG monitoring, the visualization is a labor intensive proposition, so the goal of the work herein was to develop an automated methodology that could quantify the EEG dynamics in agreement with the previously described movie's visual assessment. The basic idea is to model the STLmax topography over the scalp by means of two Gaussian functions that will be fitted to the STLmax values estimated from each scalp electrode. This Gaussian modelling of the topography is not related to the statistics of the EEG nor STLmax data in each channel, and should not be confused with statistical Gaussian mixtures since both peaks and troughs of the STLmax over the scalp are meaningful (maxima and minima of the location parameter). The approach is to fit the STLmax scalp data with both positive and negative Gaussian functions with coefficients that minimize the residual power between the fitted values and the actual STLmax values estimated from each EEG channel. Parameters of the models (centers, amplitudes and standard deviations of the Gaussians) are automatically extracted. The EEG STLmax topography was compared to the EEG power topography in two one-hour preictal EEG segments: one from a patient monitored through intracranial EEG and the other through scalp EEG, both affected by intractable epilepsy. The result of this initial study suggests that the STLmax model provided more consistent information of the epileptogenic onset zone, as determined by the neurologists.

In order to carry out a wider analysis, two more patients, also affected by intractable epilepsy were selected and each was monitored by one of the previous methods. Two patients were monitored through intracranial EEG and two through scalp EEG. Every preictal segment (1 hour before the seizure) was analyzed, STLmax was estimated and the spatial model was constructed for each of these preictal segments. The model parameters allowed for automatic extraction of information about STLmax spatial distribution for an average of 10.25 seizures per patient. Tables 1 shows the exact number of seizures per patient and therefore the duration of the analyzed EEG.

A consistent finding is that the epileptogenic onset zone appeared associated with low-STLmax levels, however, also other zones exhibited a similar behavior. A link between epileptiform behaviour and STLmax features was offered through model quantification.

The remaining part of the paper is organized as follows: Section 2 illustrates the Gaussian model and its application for STLmax topography; Section 3 reports the results of the model quantification, and the final Section 4 gives the conclusions and discussions.

2. Materials and Methods: Gaussian Modelling of STLmax topography

2.1. The data

The data were collected from four patients with medically intractable temporal lobe epilepsy: two patients (patients A and B) were monitored through multi-channel EEG scalp electrodes whereas the other two (patients C and D) were monitored through intracranial electrodes. The electrode montages are shown in Figure 1. The data were acquired by means of a Nicolet BMSI 4000/5000 recording system, the amplifiers were set in the input range of $\pm 0.6mV$ and the frequency range of the filters was set at 0.5–70Hz. The signals were sampled at 200Hz, using an analog to digital converter with 10-bit quantization, and they were finally stored. The scalp recordings contained 23 channels utilizing hemispheric derivations, according to the 10-20 system whereas the intracranial recordings are from 28 electrodes implanted in the hippocampus, temporal and frontal lobe cortices. One hour long segments preceding each seizure were extracted with a seizure detection program and verified by the technologist and the neurologist. Table I summarizes the number of seizures per patient.

2.2. STLmax estimation

In order to estimate the STLmax index for EEG signals, a modified Wolf algorithm was implemented [Iasemidis et al. 1990; 1991] to take care of possible nonstationarities present in the epileptic EEG (e.g. spikes). The window size for each STLmax calculation was 10.24 sec, embedding dimension p was set at 7 and the time lag τ was set at 20msec. The details of the STLmax algorithm and the choices of parameters are described in [Iasemidis & Sackellares 1991, Iasemidis 1991, Sackellares et al. 2000].

The STLmax (L) is estimated, for each electrode i , within each time window n obtaining an instantaneous index $L_i(n)$ with a temporal resolution of roughly 10 sec. In order to smooth the STLmax profile at each electrode i , $L_i(n)$ becomes the running mean of the vector of the five previous windows and the current one $\{L_i(n-5), \dots, L_i(n-1), L_i(n)\}$. We arranged the smoothed STLmax time series as rows of a matrix whose (i,n) element ($i=1, \dots, N$ where N is the number of electrodes) represents the STLmax value $L_i(n)$ associated with the i^{th} electrode at a certain time window n [Mammone et al. 2006]. Figure 2 shows the smoothed STLmax profiles from one scalp and one intracranial EEG channels, which look rather similar. One of the potential advantages of the smoothed STLmax technique is that the displayed information is slowly varying, therefore the differences between scalp and intracranial EEG may be less noticeable than it could be expected from an instantaneous signal analysis, as will be demonstrated later.

2.3. Gaussian Model of the STLmax topography

The goal here was to determine which electrodes were associated with the lowest and the highest STLmax values during the preictal and ictal, and to follow the evolution of the corresponding STLmax topography during these stages. Since our aim was to automatically segment each map (i.e. clustering the electrodes) so that we could extract the information about STLmax spatial distribution and then track its changes, we decided to introduce a contact transformation in order to redefine the STLmax values according to a model that could allow for the definition of proper thresholds for automatic contacts clustering. We chose a gaussian modelling (to describe with a few parameters the ever changing STLmax topography over the subject's brain areas.) and we defined two thresholds according to it, in order to cluster the electrodes in three groups: high-, medium- and low-STLmax cluster. A brief mathematical description of this model is given below:

The STLmax values over the electrodes at time n will be described by a function $f_i(n) = \tilde{L}_i(n)$ that associates with the electrode i the corresponding smoothed STLmax $\tilde{L}_i(n)$. This function is going to be approximated by a weighted sum of two Gaussian components:

$$\widehat{f}_i(n) = \sum_{k=1}^2 \alpha_k G_k(f_i(n)) \quad (1)$$

where G_i are the component densities given by:

$$G_k(f_i(n)) = \frac{1}{\sqrt{2\pi}\sigma_k} \exp\left(-\frac{(f_i(n) - \mu_k)^2}{2\sigma_k^2}\right) \quad (2)$$

where μ_k is the mean and σ_k^2 is the variance of the k -th component and α_k are the component weights. Since we are interested in modelling both the peak and the trough of the STLmax topography over the head, the component weights will not be constrained to be positive. We will compare two modelling approaches, one with the positivity constraint on the α_k 's and the other without.

For each smoothed STLmax vector $\mathbf{f}(n)$, the two values for means μ_1 and μ_2 are set at the boundaries of the range of $\mathbf{f}(n)$: μ_1 coincides with the minimum of $\mathbf{f}(n)$ and μ_2 coincides with the maximum. Then the two variances of $\mathbf{f}(n)$ (σ_1^2 and σ_2^2) around these means are estimated, imposing the positivity constraint (*model M1*). The second model constructed (*model M2*) has the same structure of *model M1*, but without the positivity constraint because it was defined as the sum of a negative Gaussian (G1) and a positive Gaussian (G2): the former centered at μ_1 and the latter centered at μ_2 . In this way, for each $\mathbf{f}(n)$ two approximations are estimated: one according to Model M1 ($\widehat{\mathbf{f}}^{M1}(n)$) and the other one according to Model M2 ($\widehat{\mathbf{f}}^{M2}(n)$). In order to pick up the best model, we compared the correlation and RMSE between $\mathbf{f}(n)$ and its approximation $\widehat{\mathbf{f}}^{Mj}(n)$ as well as their mappings.

2.3.1. Comparison of model M1 and model M2 for STLmax—The cross-correlation coefficient between the measured STLmax space vector $\mathbf{f}(n)$ at time “ n ” and its approximation $\widehat{\mathbf{f}}^{Mj}(n)$ with model *M1* or *M2* was used as a metric to compare the two modelling approaches and was computed as follows:

$$C^{Mj}(n) = \frac{\sum_{i=1}^N [f_i(n) - \bar{\mathbf{f}}(n)] \left[\widehat{f}_i^{Mj}(n) - \bar{\widehat{\mathbf{f}}}^{Mj}(n) \right]}{\sqrt{\sum_{i=1}^N [f_i(n) - \bar{\mathbf{f}}(n)]^2 \sum_{i=1}^N \left[\widehat{f}_i^{Mj}(n) - \bar{\widehat{\mathbf{f}}}^{Mj}(n) \right]^2}}$$

where i is the electrode, N is the number of electrodes, and M_j is either M1 or M2. The cross-correlation coefficient was computed for each 10.24 sec frame over all electrodes. The root mean squared error of model accuracy was also used as statistic to compare the modelling approaches and was computed as follows:

$$RMSE^{Mj}(n) = \sqrt{\frac{\sum_{i=1}^N [f_i(n) - \widehat{f}_i^{Mj}(n)]^2}{N}}$$

Table II summarizes the results of the comparison of the fitting power of the two models: the average C^{Mj} and the average $RMSE^{Mj}$. Model M2 was superior because the correlation coefficient was very close to 1.

For each time window n (i.e. column of the matrices), we plotted a 2-D map for $\mathbf{f}(n)$, a 2-D map for the approximation $\hat{\mathbf{f}}^{M1}(n)$ and a 2-D map for the approximation $\hat{\mathbf{f}}^{M2}(n)$, exploiting a function for 2-D plot from the toolbox EEGLAB [Delorme & Makeig 2004] and adapting the electrode location according to the montage used for each patient (see Figure 1).

The electrode montage is projected into a 2-D map coding the location of each electrode in polar coordinates representing the map. For each electrode, the corresponding value of $\mathbf{f}(n)$, of $\hat{\mathbf{f}}^{M1}(n)$ and of $\hat{\mathbf{f}}^{M2}(n)$ were plotted, encoding the values according to a continuous color scale going from blue (low values) to red (high values). The range of the scale was fixed so that overall variations over time could be detected as well as the local (in time) STLmax spatial distribution. The colors of the spatial points lying between the electrodes are calculated by spatial interpolation [Delorme & Makeig 2004], and thus a smooth gradation of colors is achieved.

A movie that shows STLmax topography evolution against the two modelled topographies is available at (<http://www.permano.it/research/stlmaxmapping.php>). Every frame of the movie was associated to the corresponding time, so that it was possible to keep the time information and therefore to identify the critical stages while reviewing the movie.

2.4. Model quantification

Once the best modelling approach was selected, a procedure for model quantification was required for automatic feature extraction. We aimed to extract information about the location of the brain areas related to the highest and lowest STLmax values, their spatial distribution around these areas and the evolution of their distribution over time. The first goal can be achieved by finding the spatial location of the means (centers) of the negative (G1) or of the positive (G2) fitted Gaussian components. The EEG channels closest to the centers are declared as the lowest and the highest STLmax values, respectively. For the rest of the paper, we will refer the “center of a Gaussian component” as the electrode where the center of the Gaussian component is located.

In order to pick the brain areas most often associated with the minimum and maximum STLmax values during the observed intervals, we simply counted how often each electrode is the center of G1 and how often it is the center of G2, normalized by the number of windows in the analyzed recording. This relative frequency is indeed a probability of observing the respective Gaussian center at that location over time. The relative frequency will be represented as frequency bar graphs where on the x-axis one finds the electrodes and on the y-axis one finds the relative frequency of observing the respective Gaussian center at a certain electrode.

We are not only interested in the minimum and maximum STLmax values, but also in localizing over the scalp the low- and high-STLmax areas. Thus, for each time window, the electrodes are clustered according to their proximity to the trough value of the G1 component or to the peak value of the G2 component using two thresholds, η_1 and η_2 . The electrodes whose modelled values were lower than the threshold η_1 were clustered in the “negative” cluster CL1 (thus associated with low STLmax), and the electrodes whose modelled values were higher than the threshold η_2 were clustered in the “positive” cluster CL2 (thus associated to high STLmax). The remaining electrodes were clustered in the “neutral” cluster CL3 (associated with medium STLmax). In order to quantify this clustering, we counted how often each electrode belonged to CL1 or to CL2, over modelling windows. The two thresholds, η_1 and

η_2 , were defined as the inflection points of a Gaussian $\mu \pm \sigma$, where μ is the mean and σ is the variance. We defined the two thresholds, η_1 and η_2 as follows:

$$\eta_1 = \mu_1 + \frac{\sigma_1}{k} \text{ and } \eta_2 = \mu_2 - \frac{\sigma_2}{k} \quad (3)$$

where k is a scaling factor to reduce the possibility of crossing between η_1 and η_2 and ensure that $\eta_1 \leq \eta_2$, $k=3$ avoided any crossing in our data set, however, in the case of a crossing, the zero threshold η_0 (crossing point between G1 and G2) will be selected by the algorithm as the unique threshold for two clusters only (CL1 and CL2), i.e.:

$$\eta_0 = \frac{-2(\mu_2\sigma_1^2 - \mu_1\sigma_2^2) + 2\sqrt{(\mu_2\sigma_1^2 - \mu_1\sigma_2^2) + (\sigma_2^2 - \sigma_1^2)\left[\mu_1^2\sigma_2^2 + \mu_2^2\sigma_1^2 + 2\sigma_1^2\sigma_2^2\log(\sigma_1/\sigma_2)\right]}}{2(\sigma_2^2 - \sigma_1^2)} \quad (4)$$

The relative frequency of the membership to clusters will be represented as a map: the electrodes will be represented with black dots whereas the membership will be coded with a coloration going from dark blue, for a high relative frequency of membership to cluster CL1 (low-STLmax), to dark red, for a high relative frequency of membership to cluster CL2 (high-STLmax). Yellow and green coloration means membership to cluster CL3.

3. Results

3.1. Comparison of STLmax and EEG power modelling

First of all, the performance of the model based on STLmax topography was compared with that based on the EEG power topography. We selected one one-hour preictal EEG segment from a patient monitored through scalp EEG (patient A) and one one-hour preictal EEG segment from a patient monitored through intracranial EEG (patient D). The STLmax and EEG power were both estimated with 10.24sec non-overlapping EEG segments. The power of each EEG channel was downsampled to the STLmax time resolution within 1min moving windows, in order to get a smooth and comparative profile. The EEG power time series were arranged as rows of a matrix, as explained in Section 2.2 for STLmax. Both EEG power and STLmax were modelled as described in Section 2.3, and quantified according to Section 2.4.

3.1.1. Comparison for scalp EEG (patient A)—Electrographically, the selected preictal segment is characterized by active epileptiform potentials consisting of moderate voltage spike and wave complexes appearing independently in the right front-temporal as well as the left front-temporal regions. The ictal EEG exhibited bilateral high amplitude rhythmic delta activity that was higher on the left side. This event represented a complex partial seizure without secondary generalization, with localization to the left mesial anterior temporal lobe.

STLmax modelling (Figure 3.a.2 and Figure 4.a.2) suggests a relationship between the area active during the ictal stage (left mesial anterior temporal lobe) and the most probable center (see electrode A1 in Figure 3.a.2) of the first Gaussian component G1. In general, there is also a relationship with the most active electrodes in cluster CL1 (the left temporal zone is dark blue in Figure 4.a.2) in the quantification of STLmax modelling. Figures 3.a.2 and 4.a.2 also suggest a link between the area of preictal epileptiform activity (fronto-temporal region) and the most probable center of the second Gaussian G2 (FP1, see Figure 3.a.2) and in general the positive cluster CL2 (FP1, FP2, F7, F8 belong to the red area in Figure 4.a.2).

EEG power modelling (Figure 3.a.1 and Figure 4.a.1) yielded similar results because it also showed a left lateralization of the most probable center of G1 (see electrode P3 in Figure 3.a.1) albeit it is a bit more far away from the location of ictal activity (left mesial anterior temporal lobe) compared to A1, the center of G1 according to STLmax modelling. Figure 4.a.1 shows a link between cluster CL1 (blue areas in Figure 4.a.1) and the ictal zone, except for the central zone that appears in a blue coloration but is not involved in epileptiform activity. There is no relationship of the area of preictal epileptiform activity (fronto-temporal region) with the most probable center of Gaussian G2 (electrode O2) and just a weak relationship with the positive cluster CL2 (electrodes F3, C3, O2, Fz).

3.1.2. Comparison for intracranial EEG (patient D)—Electrographically, the event came from the right mesial temporal lobe (RD2 and RD4) with an involvement of the left temporal lobe (LT) and of left OF.

The most probable center of the Gaussian component G1 (channels RD2, LT2, see Figure 3.d.2) and, in general, the most active electrodes in cluster CL1 (channels RD2, RD4, LT2 and LF4, see Figure 4.d.2) seems to be linked to the area active during the ictal stage (RD2, RD4, left temporal lobe and left OF) according to the STLmax based modelling.

If modelling and quantification are carried out over EEG power, no link between the ictal onset area with the most probable center of the first component G1 (RD12, LF3, see Figure 3.d.1) can be seen and just a weak link, through LT2, with the most active electrodes in cluster CL1 (LT2, RT4, LF2, LF3, see Figure 4.d.1) can be detected.

3.1.3. Statistical analysis of the comparison between STLmax and EEG power modelling—It seems that, for intracranial recordings, the results yielded by STLmax modelling differ a lot from those yielded by EEG power based modelling, whereas this difference becomes less evident for scalp EEG. However, STLmax mapping seem to provide more information about the onset zones than the modelling of EEG power does. In particular, cluster CL1 seems to be able to make the underlying abnormality of the onset zone appear, even one hour before the seizure onset, even though also other zones exhibit the same relationship with cluster CL1. In order to verify this statement, we carried out a hypothesis test that will be described in this Section. From now on, we will name STLmax and EEG power as the “mapping parameter” and we will compare the results of the statistical test carried out on EEG power and STLmax modelling, respectively.

Let us define $\tau_i^{CL1}(w)$ as the average frequency of membership of the onset zone electrode “i” to Cluster CL1 within a 10-min time window w , where $w = 1 \dots M$ and M is the number of overlapping windows in a 1 hour preictal data segment, with a 10.24 sec overlap (see Section 3.1). The width 10min was chosen in order to estimate the average frequency within a sufficiently wide window and the shift ahead was chosen 10.24, just one STLmax sample, in order to come up with a smooth trend of the average frequency.

Starting from the hypothesis that we aim to verify, an alternative hypothesis was formulated as follows:

ALTERNATIVE HYPOTHESIS H1: The electrodes of the onset zone belong to cluster CL1 (low-mapping parameter levels) with a higher frequency, compared to the overall average frequency of membership to CL1, throughout the 1hour preictal segment under analysis. In other words: $\tau_i^{CL1}(w)$ is the average frequency of membership of onset zone electrode “i” to Cluster CL1 within a 10-min time window w and if $\bar{\tau}_{all}^{CL1}(w)$ is the average frequency of

membership of all the electrodes to the same cluster, then $\tau_i^{CL1}(w) > \bar{\tau}_{all}^{CL1}(w)$ (one-tailed hypothesis).

We will test H1 against the NULL HYPOTHESIS H0: $\tau_i^{CL1}(j) \approx \bar{\tau}_{all}^{CL1}(j)$.

Chosen a preictal 1-hour segment for patient A and a preictal 1-hour segment for patient D, for each overlapping window w , $\tau_i^{CL1}(w) - \bar{\tau}_{all}^{CL1}(w)$ was estimated. This way we obtained a matrix **T** per patient whose elements are: $T(i, w) = \tau_i^{CL1}(w) - \bar{\tau}_{all}^{CL1}(w)$. The single row represents a population **T_i** of M elements where M is the number of windows:

$$T_i = \{\tau_i^{CL1}(1) - \bar{\tau}_{all}^{CL1}(1), \dots, \tau_i^{CL1}(M) - \bar{\tau}_{all}^{CL1}(M)\}.$$

In order to test the null hypothesis, we first tested the normality of the distribution of the populations **T_i** exploiting the Shapiro–Wilk test (Shapiro and Wilk 1965). It tests the null hypothesis that a sample comes from a normally distributed population.

$T_i = \{\tau_i^{CL1}(1) - \bar{\tau}_{all}^{CL1}(1), \dots, \tau_i^{CL1}(M) - \bar{\tau}_{all}^{CL1}(M)\}$ is our sample and the test was carried out over each **T_i** in order to assess if the population of electrode i could be considered normally distributed. The result of the normality test was that no population was normally distributed thus the Wilcoxon test (one-tailed) was adopted. H0 is rejected if the result of the test is above the critical threshold that was obtained from the table of the critical values of the Wilcoxon Signed Ranks Test (for $n=M$, where $M > 100$ is the number of overlapping windows and $\alpha = 0.05$, the critical threshold is 151).

Looking at Figure 5 we can see that, for patient A, the electrodes that rejected H0 when the modelling was based on EEG power (Figure 5.a.1) are: T7, P3, Cz, A1, and the electrodes that rejected H0 when the modelling was based on STLmax (Figure 5.a.2) are: T7, P3, P4, O1, O2, A1 and A2. The onset zone (left temporal area) is included in either one of the two groups of electrodes, so STLmax is not particularly superior.

For what concerns patient D, the electrodes that rejected H0 when the modelling was based on EEG power (Figure 5.d.1) are: RD8, RD12, LT2, RT2, RT3, RT4, LF2, LF3, RF2 and RF3, whereas the electrodes that rejected H0 when the modelling was based on STLmax (Figure 5.d.2) are: RD2, RD4, LT1, LT2 and LF4. The onset zone is fully included in the second group whereas the first group completely missed RD2 and RD4 that are the electrodes where seizures mainly originated, therefore STLmax was far superior in this case. A summary of this statistical analysis is provided in Table III.

In conclusion, we chose STLmax based modelling because it appeared sensitive to the activity of the onset zone when estimated from either scalp or intracranial EEG.

3.2. STLmax topography modelling of four patients

In order to quantify further the STLmax topographic model performance, we chose the preictal segments one hour before each seizure, which corresponds to over 10.5 hours per patient on average. We analyzed the model within each preictal segment and then the average overall behaviour was extracted through clustering as explained in Section 2.4.

The model quantification results will be discussed patient by patient. As described in the previous Section, the most probable centers (% of time spent) are represented by frequency bar graphs in Figure 6 whereas, in order to easily observe the spatial distribution of STLmax, the membership degree to cluster CL1 (low-STLmax) and to cluster CL2 (high-STLmax) is depicted in Figure 7 through maps that represent the average spatial distribution (from all the

1-hour preictal segments) of Cluster CL1 and Cluster CL2 according to STLmax modelling. Each sub-picture k in Figure 7 is associated with patient k . The electrodes are represented with black dots whereas the membership to clusters was colour coded from dark blue, for a high relative frequency of membership to cluster CL1, to dark red, for a high relative frequency of membership to cluster CL2. Yellow and green mean membership to cluster CL3.

3.2.1. Patient A (scalp EEG)—The electrographical review of the interictal segments reports active epileptiform potentials consisting of moderate voltage spike and wave complexes recorded independently from the right front-temporal region as well as the left front-temporal region with a ratio of right to left of 50:50. Every event appeared bilaterally from the anterior temporal lobes (with a predominance in amplitude to the left), except the first event (seizure induced by hyperventilation) that had a balanced onset and that was non-lateralizing, all the events localized on the left anterior mesial temporal lobe.

Figures 6.a and 7.a, depict the results of the average model quantification: Figure 6.a shows the average centers and Figure 7.a shows the average results of clustering. Globally, A1 was detected as the most probable center for the first Gaussian component G1 (i.e. center of lowest STLmax activity), P3 and P4 were very common centers as well. Thus the temporal area (linked to the epileptogenic onset zone) seems to “attract” the centers of G1.

For what concerns the results of clustering, Patient A had an onset zone in the left temporal lobe which showed a high membership to cluster CL1 (blue area in Figure 7.a) together with an area between electrodes P3 and P4, whereas the fronto-temporal zone belonged to cluster CL2 (red area in Figure 7.a) thus the onset zone belonged to cluster CL1 but it is worth to point out also a “dipole effect” with the left frontal-temporal area.

3.2.2. Patient B (scalp EEG)—For this patient every event rose bilaterally, as well as interictal spikes and waves, and was non-localizing. We found out that A2 was the average most probable center of G1 (top of Figure 6.b), however, there is not a clear localization of the center of G1 whereas the center of G2 gravitates around the frontal area. The low-STLmax area seems to move from the left temporal region to the right one and vice versa, crossing the central lobe. Even though a specific onset zone could not be identified for patient B, the STLmax model shows evidence of bilateral activity, as we can see from the topography of the membership to cluster CL1 and CL2 that appears balanced between the right and the left hemisphere (Figure 7.b).

3.2.3. Patient C (intracranial EEG)—Electrographically, the interictal segments of patient C are characterized by active spikes and wave activities coming from the right and left orbital frontal regions. All the events came from the right hippocampus, in particular from RD2, the right sub-temporal leads were always soon involved (strip RT). Interictal activity involved ROF and LOF.

Looking at the quantification of the distribution we can verify that the RD2 and RT leads, together with LD7 and LD9, were most of the time associated with low-STLmax. In fact Figure 6.c (top) shows that the average most probable center of G1 was LD9 but RD2, RT2, RT3, RT4 and also LD11 were the electrodes most of the time involved in cluster CL1 (blue areas in Figure 7.c), therefore they were strongly linked to low-STLmax. Left temporal depths (LD) did not show electrographical relationship with the onset.

In conclusion, Patient C had events that came from the right hippocampus, in particular from RD2, with an involvement of the right sub-temporal leads (RT) and the membership of these areas to cluster CL1, throughout the 1hour preictal segments, is clearly visible as the blue spots

in Figure 7.c. However, we also noticed that also LD9 showed an involvement in cluster CL1 but it was not identified as an onset zone electrographically.

3.2.4. Patient D (intracranial EEG)—Electrographically, inter-ictal spikes and waves came from right temporal depths (RD), with an involvement of left sub-temporal (LT) and intermittently from orbital-frontal. Every event came from the right mesial temporal lobe (RD2 and RD4) with an involvement of the left temporal lobe (LT) and left orbital-frontal (LF).

Figure 6.d shows the average most probable centers of the two components in the model quantification. RD2 attracted the center of G1 (top of Figure 6.d), and so did LT2, even though it was less predominant. RD2 and LT2 are definitely the average most probable centers. LD1 is the center of G2 (bottom of Figure 6.d).

Patient D has sharp topography of the membership to the three clusters (Figure 7.d): the onset zones (RD2, RD4, LT and LF) showed high membership to cluster CL1 throughout the 1-hour preictal segments, in fact, blue spots are clearly visible in the map.

3.3. Statistical analysis

The results suggest that cluster CL1 (low-STLmax) was dominated by electrodes of the onset zone throughout the entire preictal segments. This might mean that a background abnormality in STLmax spatial distribution is detectable in the onset zone even 1 hour before the seizure onset. In order to verify this hypothesis, we carried out a hypothesis test that will be described in this Section. Starting from the hypothesis that we aim to verify, an alternative hypothesis was formulated as follows:

ALTERNATIVE HYPOTHESIS H1: The electrodes of the onset zone belong to cluster CL1 (low-STLmax levels) for a longer time compared to the overall average time, throughout the entire 1-hour preictal j -th segment. In other words: if $\tau_i^{CL1}(j)$ is the relative time an onset zone electrode i spends in Cluster CL1 during a 1-hour preictal segment j and if $\bar{\tau}_{all}^{CL1}(j)$ is the average relative time spent by all the electrodes in the same cluster, then $\tau_i^{CL1}(j) > \bar{\tau}_{all}^{CL1}(j)$ (one-tailed hypothesis).

We will test H1 against the NULL HYPOTHESIS H0: If $\tau_i^{CL1}(j)$ is the relative time an onset zone electrode i spends in Cluster CL1 during a 1-hour preictal segment j and $\bar{\tau}_{all}^{CL1}(j)$ is the average relative time spent by all the electrode in the same cluster, then $\tau_i^{CL1}(j) \approx \bar{\tau}_{all}^{CL1}(j)$.

For each patient, for each preictal 1-hour segment “ j ” and for each electrode “ i ”, $\tau_i^{CL1}(j) - \bar{\tau}_{all}^{CL1}(j)$ was estimated. This way we obtained a matrix **T** per patient whose rows represented the electrodes and whose columns represented the preictal segments. The single row represents a population **T_i** of M elements where M is the number of preictal segments:

$$T_i = \{\tau_i^{CL1}(1) - \bar{\tau}_{all}^{CL1}(1), \dots, \tau_i^{CL1}(M) - \bar{\tau}_{all}^{CL1}(M)\}.$$

In order to test the null hypothesis, we first tested the normality of the distribution of the populations **T_i** exploiting the Shapiro–Wilk test [Shapiro and Wilk 1965]. It tests the null hypothesis that a sample comes from a normally distributed population.

$T_i = \{\tau_i^{CL1}(1) - \bar{\tau}_{all}^{CL1}(1), \dots, \tau_i^{CL1}(M) - \bar{\tau}_{all}^{CL1}(M)\}$ is our sample and the test was carried out over each **T_i** in order to assess if the population of electrode i could be considered normally distributed. The results of the normality test are reported, for each patient k , in Table IV.k.

Since most of the electrodes fulfilled the normality test, except patient B, one tailed T-test was applied. Nonparametric Wilcoxon test was used for patient B.

The decision rule is: Reject H_0 if

$$\frac{\bar{T}_i}{\frac{\sigma_{T_i}}{\sqrt{M}}} > t_{M-1, \alpha} \quad (5)$$

with $\alpha = 0.05$ with $M-1$ degrees of freedom.

This statistical test was performed for each patient, for each preictal 1-hour segment “j” and for each electrode “i” and is summarized in Figure 8: the electrodes whose levels lie above the threshold are those that, statistically, belonged to cluster CL1 (low-STLmax levels) for a longer time compared to the overall average time, throughout all the preictal segments.

Looking at Figure 8.a we can point out that, for patient A, the null hypothesis was rejected by electrodes A1, P7, O2, O1, therefore by the left temporal region with an involvement of the occipital lobe. We noticed that electrode T7, that belongs to the left temporal lobe, showed membership to the neutral cluster CL3 (green coloration in Figure 8.a), thus it did not help localizing the onset zone. In the future, a wide group of scalp EEG recordings will be analyzed in order to ascertain if every electrode of the onset zone is involved in cluster CL1 throughout the preictal stages or not.

For patient B, the normality distribution was not fulfilled by most of the electrodes and, therefore, the Wilcoxon test (one-tailed) was adopted. H_0 is rejected if the result of the test is above the critical threshold that was obtained from the table of the critical values of the Wilcoxon Signed Ranks Test (for $n=M$, where $M=14$ is the number of preictal segments for patient B, and $\alpha = 0.05$, the critical threshold is 25). Observing Figure 8.b, we can say that the electrodes that rejected H_0 are: T7, T8, P7, P8, P3, Cz, A2. For this patient every event rose bilaterally and was non-localizing, there is not a specific onset zone but the results of the statistical analysis endorse the presence of bilateral activity.

For patient C, the normality distribution was fulfilled by most of the electrodes and the T-test shows that the null hypothesis was rejected by electrodes RD2, RT2, RT3, LD9 and LD11, thus by the electrodes of the onset zone with an involvement of electrode LD9 and slightly of LD11.

For patient D, the normality distribution was fulfilled by most of the electrodes and the T-test shows that null hypothesis was rejected by electrodes RD2, RD4, LT2 and LF3, thus by electrodes of the onset zone.

A summary of this statistical analysis is provided in Table V.

This statistical test endorses the hypothesis that cluster CL1 (low STLmax) was generally dominated by electrodes of the onset zone throughout the entire preictal segments and this suggests that a background abnormality in STLmax spatial distribution can be detectable in the onset zone even 1 hour before the seizure onset.

4. Discussion and conclusions

This paper models STLmax based brain topography and presents results on four patients affected by intractable temporal lobe epilepsy. Two patients were monitored through scalp

EEG and the other two through intracranial electrodes for 10.5 hours on average. The multi-electrode EEG data were processed by the STLmax algorithm, and a topography of these STLmax profiles was constructed to produce a spatio-temporal evolution of the profiles over the brain. Furthermore, the topography was fitted by a multi-Gaussian model in order to automatically extract information about STLmax spatial distribution over time. The quantification was based on the localization of the two centers (to detect the electrode location of peaks and troughs of activity) and on the identification of three clusters to determine if an electrode belonged to the area of large STLmax activity, low STLmax activity or was kind of neutral.

The quantification of the model suggests a relationship between the onset zone and low-STLmax levels long before the seizure onset, in both scalp and intracranial EEG. For a data set built from one hour preictal data segments preceding every seizure, the focal area was shown generally linked to the center of the low STLmax Gaussian component, and also to the most active electrodes of this cluster. Surprisingly, the spatial location of low STLmax activity was very stable over the head even one hour before the seizure onset, which means that the focal signature may exist long before the seizure onset.

STLmax topography modelling of scalp and intracranial EEG seems to provide similar results, in fact, the epileptogenic onset zone appear linked low-STLmax levels long before the seizure onset in both analyses, as endorsed by the statistical tests. Thus the deep difference in signal structure between EEG and ECoG does not seem to affect modelling results, however, it is worth pointing out that the results yielded by intracranial analysis are sharper, probably because they do not suffer from the volume conduction averaging embedded in the EEG. Basically, looking at the quantification of intracranial EEG, there are just a few electrodes linked to the center of the low STLmax Gaussian thus the histogram is very peaky, whereas, in scalp analysis the histogram is much smoother.

In conclusion, our method showed to be able to detect, from the very beginning of the analyzed one-hour preictal segments, an abnormal behavior of the cerebral onset zones: a persistent and steady concentration of low-STLmax levels. However, sometimes areas other than the focal ones showed similar behavior. The method was successful in onset zone localization in 3 out of 4 patients: 1 out of 2 of scalp patients and 2 out of 2 in intracranial patients. Future research will be focused on finding out the reason of these “false positives”, in fact, the goal will be finding out if they are real false positives or if we are in presence of areas that not involved in the onset but that are somehow involved in the network phenomena that lead to seizures. In order to do that, we might have either to introduce a more sophisticated model or to optimize the model of STLmax spatial distribution, or even to replace STLmax as a descriptor of brain dynamics. Therefore, even though our method is still not suitable for preventive automatic onset zone localization, it is a good starting point for developing such a tool because this paper showed that STLmax spatial distribution is not random but is correlated to epileptiform activity, even one hour before the seizure onset. Furthermore, our future goal is not limited to focus localization but is extended to detecting and quantifying the global dynamical changes that result in a seizure by continuously tracking the ongoing temporal changes in spatial patterns of EEG.

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Figure 1.

Scalp electrode montage (a.1) and Intracranial electrode montage (b.1). The scalp electrode montage has been schematized, for mapping purposes, as shown in Figure a.2 whereas the intracranial electrode montage has been schematized as shown in Figure b.2.

Figure 2.
Smoothed STLmax profile of two critical electrode sites: (a) electrode T7 of patient A; (b) electrode RD2 of patient D.

Figure 3.

Modelling of a 1 hour segment preceding a seizure from Patient A and Patient D. **Patient A:** most probable centers of the Gaussian Components G1 and G2 according to the modelling of: (a.1) EEG power; (a.2) STLmax. **Patient D:** most probable centers of the Gaussian Components G1 and G2 according to the modelling of: (d.1) EEG power; (d.2) STLmax. The relative frequency of observing the respective Gaussian center at a certain electrode location over time will be represented as frequency bar graphs where on the x-axis one finds the electrodes and on the y-axis one finds the relative frequency of observing the respective Gaussian center at a certain electrode.

Figure 4.

Modelling of a 1hour segment preceding a seizure from Patient A and Patient D according to EEG power and STLmax. **Patient A:** clustering of the electrodes according to the modelling of: (a.1) EEG power; (a.2) STLmax. **Patient D:** clustering of the electrodes according to the modelling of: (d.1) EEG power; (d.2) STLmax.

The electrodes are represented with black dots whereas the membership to clusters was coded with a coloration going from dark blue, for a high relative frequency of membership to cluster CL1, to dark red, for a high relative frequency of membership to cluster CL2. Yellow and green mean membership to CL3.

Figure 5.

Statistical comparison of modelling based on EEG power and STLmax. Figure 5.k.1 shows the results, for patient k , based on EEG power modelling whereas Figure 5.k.2 shows the results based on STLmax modelling. H_0 is rejected if the result of the test is above the critical threshold that was obtained from the table of the critical values of the Wilcoxon Signed Ranks Test (for $n=M$, where $M > 100$ is the number of overlapping windows and $\alpha = 0.05$, the critical threshold is 151).

Figure 6.

Average centers of the Gaussian Components G1 and G2 according to STLmax modelling of: (a) patient A; (b) patient B; (c) patient C; (d) patient D. The relative frequency of observing the respective Gaussian center at a certain electrode location over time will be represented as frequency bar graphs where on the x-axis one finds the electrodes and on the y-axis one finds the relative frequency of observing the respective Gaussian center at a certain electrode.

Figure 7.

Synthetic maps that represent the average (with respect to all the 1hour preictal segments) spatial distribution of Cluster CL1 (blue areas in submaps “a”) and Cluster CL2 according to STLmax modelling of: (A) patient A; (B) patient B; (C) patient C; (D) patient D.

The electrodes are represented with black dots whereas the membership to clusters was coded with a coloration going from dark blue, for a high relative frequency of membership to cluster CL1, to dark red, for a high relative frequency of membership to cluster CL2. Yellow and green mean membership to CL3.

Figure 8.

Results of the statistical test. Sub-Figure k reports the results of the statistical test for patient k . The electrodes whose levels are over the threshold are those that, statistically belonged to cluster CL1 (low-STLmax levels) for a longer time compared to the overall average time, throughout all the preictal segments, thus rejected H_0 .

Table I

Number of 1hour preictal segments analyzed per patient.

Patient	Number of 1hour preictal segments analyzed
Pat A	9
Pat B	14
Pat C	7
Pat D	9

Table II

Comparison of the fitting power of Model M1 and Model M2.

Patient	Model			
	Model M1		Model M2	
	C^{M1}	mean $RMSE^{M1}$	C^{M2}	mean $RMSE^{M2}$
Patient A	0.82	3.65	0.99	3.31
Patient D	0.68	4.38	0.99	4.01

Table III

Comparison between STLmax and EEG power modelling: comparison between the onset zone and the electrodes that dominated cluster CL1 (low-EEG power/low-STLmax levels). There is a significant match between the onset zone and the electrodes that rejected hypothesis H0 (hypothesis H0 = they did not belong to cluster CL1 for a longer time compared to the overall average time, within the analyzed 1hour preictal segment) for Patient A either with EEG power and STLmax based modelling. For patient D, EEG power based modelling did not perform well: only the orbital-frontal electrodes fell in the low-EEG power cluster, whereas there is a significant match between the onset zone and cluster CL1 according to STLmax based modelling.

	Onset Area	Low-EEG Power Electrodes (Cluster CL1)	Low-STLmax electrodes (Cluster CL1)
Patient A	Anterior temporal lobes (with a predominance in amplitude to the left) with localization on the left anterior mesial temporal lobe.	T7, P3, Cz, A1	T7, P3, P4, O1, O2, A1 and A2
Patient D	Right mesial temporal lobe (RD2 and RD4) with an involvement of the left temporal lobe (LT) and left orbital-frontal (LF)	RD8, RD12, LT2, RT2, RT3, RT4, LF2, LF3, RF2 and RF3	RD2, RD4, LT1, LT2 and LF4

TABLE IV

TABLE IV.A

Results of the shapiro-wilk test for gaussianity for patient A

label	FP1	FP2	F7	F8	F3	F4	T7	T8	C3	C4	P7	P8	P3	P4	O1	O2	Fz	Cz	A1	A2
Gaussian/Non Gaussian	G	NG	G	G	G	G	G	G	G	G	G	G	NG	G	G	G	NG	NG	G	G

TABLE IV.B

Results of the shapiro-wilk test for gaussianity for patient B

label	FP1	FP2	F7	F8	F3	F4	T7	T8	C3	C4	P7	P8	P3	P4	O1	O2	Fz	Cz	A1	A2
Gaussian/Non Gaussian	G	NG	NG	NG	NG	NG	NG	G	G	NG	NG	NG	G	NG	NG	NG	NG	G	NG	G

TABLE IV.C

Results of the shapiro-wilk test for gaussianity for patient C

label	LD1	LD3	LD5	LD7	LD9	LD11	RD2	RD4	RD6	RD8	RD10	RD12	LT1	LT2	LT3	LT4	RT1	RT2	RT3	RT4	LF1	LF2	LF3	LF4	RF1	RF2	RF3	RF4
number	G	G	G	NG	NG	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	NG	G	G

TABLE IV.D

Results of the shapiro-wilk test for gaussianity for patient D

label	LD1	LD3	LD5	LD7	LD9	LD11	RD2	RD4	RD6	RD8	RD10	RD12	LT1	LT2	LT3	LT4	RT1	RT2	RT3	RT4	LF1	LF2	LF3	LF4	RF1	RF2	RF3	RF4
number	G	G	G	G	G	G	G	G	G	NG	G	G	NG	G	NG	NG	G	G	G	G	G	NG	G	G	G	NG	NG	G

Table V

Summary of the statistical analysis of the performance of STLmax modelling: comparison between the onset zone and the electrodes that dominated cluster CL1 (low-STLmax levels). There is a significant match between the onset zone and the electrodes that rejected hypothesis H0 (hypothesis H0 = they did not belong to cluster CL1 for a longer time compared to the overall average time, throughout each 1hour preictal segment).

	Onset Zone	Low-STLmax electrodes (Cluster CL1)
Patient A	Anterior temporal lobes (with a predominance in amplitude to the left) with localization on the left anterior mesial temporal lobe	A1, P7, O2, O1
Patient B	Every event rose bilaterally, as well as inter-ictal spikes and waves, and was non-localizing	T7, T8, P7, P8, P3, Cz, A2
Patient C	Right hippocampus, in particular from RD2, the right sub-temporal leads were always soon involved (strip RT)	RD2, RT2, RT3, LD9 and LD11
Patient D	Right mesial temporal lobe (RD2 and RD4) with an involvement of the left temporal lobe (LT) and left orbital-frontal (LF)	RD2, RD4, LT2 and LF3