AUTOMATIC LATERALIZATION OF TLE BASED ON NON-LINEAR CORRELATION ON SCALP EEG: STUDY ON 43 PATIENTS

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Abstract: The objective of this work is to characterize the way epileptic seizures are initiated using scalp ElectroEncephaloGram (EEG) and to use this analysis for lateralization of temporal seizure onset zone. A comprehensive method based on the evaluation of synchronization degree between cerebral regions at seizure onset is presented. The synchronization is measured by non-linear regression analysis of surface EEG signals. Results show that comparison of mean level of correlation at seizure onset, on a certain number of channels, provides an efficient indication of lateralization.

Introduction

Temporal Lobe Epilepsy (TLE) is the most common form of partial epilepsy. It can generally be medically treated but about 20 to 25% of patients are drug resistant. In about half of them temporal lobectomy may be the therapeutic alternative. Localization of epileptic seizure onset zone, that is defined has the part of brain were seizures are generated, is thus important before considering surgical operation [1, 2, 3].

Several techniques are used to realize a reliable evaluation when epilepsy is diagnosed, such as interictal and video-EEG monitoring, MRI, PET, SPECT, and neuropsychological assessment. Among these techniques EEG remains one of the best evaluation tool, particularly for lateralization of seizure onset [4, 5]. When comparing other methods to scalp EEG lateralization, variable results are observed, but all different research teams show results around 80% to 95% of concordant side detection [6, 7].

All these techniques are based on visual inspection because automation of the process remain a difficult problem that has not been thoroughly addressed, up to now. In fact, scalp EEG signals are difficult to automatically analyse because of all artefacts that affect it from its generation in neurons to its recording on scalp electrodes.

The present study is focused on the research of an automatic lateralization of the epileptogenic zone defined as the region primarily involved at seizure onset. At the onset of a seizure, rhythmic waves can be interpreted as specific patterns in lateralization [8], that reflects some synchronization between cerebral regions. This degree of synchronization is estimated in SEEG by non-linear regression analysis [9, 10].

In this study we applied this technique to scalp EEG, assuming that increase in synchronicity is the reflect of the same phenomenon that in SEEG. Our main hypothesis is that the correlation between rhythmic activities is more important on the side of the seizure onset. If so, seizure onset time has to be identify and a measure of difference between mean of correlation from each side of the brain on a window can point out the lateralization of seizure onset zone.

Materials and Methods

43 patients with TLE who underwent long-term scalp EEG were included in the study. They are aged from 16 to 45 years old. After a complete pre-surgical evaluation, including, the diagnosis for all of them was a partial Temporal Lobe Epilepsy (TLE).

For each patient, two seizures were selected (three for one patient). All data files were annotated by two neurologists, so that seizure onset time and the seizure lateralization is known. No other selection criteria that having approximately as many left than right seizures and presence of a partial TLE were applied, so that certain data contain many artefacts.

EEG signals were recorded according to 10/20 system (24 channels) and sampled at 512 Hz. Signals were digitally filtered in the 0.5-30Hz band and sub sampled to 256Hz, in order to improve the signal processing time. The montages, used for recording EEG signals in this paper, are all longitudinal. This choice has been made for at least two major reasons: it reduces influence of the reference on signal processing and, in a differential montage, the localization of an event source is given by the "orientation" of EEG signals, which is less disrupted by artefacts than its amplitude.

In order to reduce the very large amount of data produced by video-EEG monitoring, we chose eight electrode couples for each side of the brain in the longitudinal montage to apply lateralization algorithms. These

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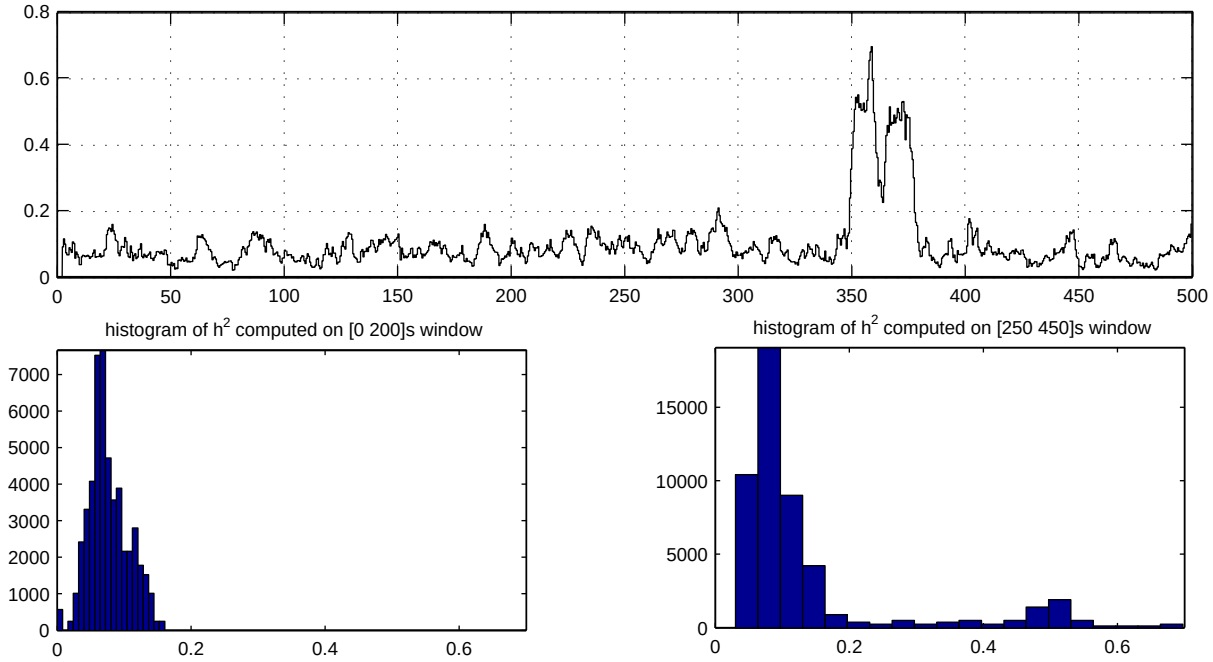

Figure 1: On the figure 1a), h^2 coefficient is presented. Seizure onset is indicated by the neurologist on corresponding EEG at 350s. On the figure 1b), histogram of pre-ictal part of the signal is presented (computed on 0-200s). One can see, that correlation value are never higher than 0.18. On the figure 1c), histogram of the signal around the seizure is presented (computed on 250-450s). Most part of correlation values are under 0.18, but those extracted from seizure that are around 0.5.

couples were selected with the help of the neurologist to keep a good spatial sampling of the temporal lobe regions of interest.

The synchronization degree between brain regions was measured using a non-linear regression method, following the equation:

$$h^{2^*}_{XY} = 1 - \frac{\sum_{n=1}^{N}(y_n - \hat{\mu}_{XY}(x_n))^2}{\sum_{n=1}^{N}(y_n - \bar{y})^2}, \qquad (1)$$

where $\hat{\mu}_{XY}(x_n)$ is the linear piecewise approximation of the regression curve between channel X and X of the EEG, and $\bar{y}$ is the average of y over the N points of the windowed signal.

The computation of $h^2_X Y$, is reiterated for different values of a time shift τ between x and y. The use of this time shift gives the information of the delay between both signals.

$$h^2_{XY} = \max_{\tau_{min}<\tau<\tau_{max}} [h^{2^*}_{XY}(\tau)], \qquad (2)$$

The values of h^2_{XY} are comprised between 0 (Y is independent of X)and 1 (Y is linearly or non-linearly dependent of X). In case of linear relationship between X and Y, h^2_{XY} reduce to common Pearson linear correlation coefficient r^2_{XY} [11]. All combinations between the 8 scalp electrodes for each side of the brain were computed.

h^2_{XY} is computed on a 5s sliding window, as $X(t)$ and $Y(t)$ are considered quasi stationary, with an overlap of 0.5s. $h^2_{XY}(t,\tau)$ was calculated for all values of delay τ included in an interval $[-40\ 40]ms$ around current time t, and only the maximum value for each $h^2_{XY}(t,\tau)$ was kept.

To apply lateralization algorithm, seizure onset time has to be indicated. So, detection of epileptic events was performed by to ways using h^2 coefficient. On one hand was a manual indication of seizure onset based on neurologists indication. On the second hand, beginning of seizure was semi-automatically extracted from h^2 signals. A mono-channel detector is applied to each h^2_{XY} signals averaged over a time window. When a threshold computed over the period that precedes seizure is reached, a detection instant is marked. It is defined from a combination of the mean and standard deviation of h^2. In a second time, a multi-channel detector is applied to data. When an instant is marked on more than three h^2 channels, an epileptic event is considered probable. If several events are detected, they are classified according to the highest h^2 energy on a 30s window after event beginning. The one that corresponds to the real one is kept, other are discarded. If the epileptic event could not be defined by this way, manual seizure onset time is used.

Once the onset is marked (manually or semi-automatically), the sum of the values of h^2 for each side are compared on a window and the indice S_{ide} is computed:

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$$S_{ide} = sign\left(\sum_{i,j\neq i}\sum_{k=beg}^{end} h^{2_{right}}_{X_iY_j}(k) - \sum_{i,j\neq i}\sum_{k=beg}^{end} h^{2_{left}}_{X_iY_j}(k)\right) \quad (3)$$

Where, *beg* and *end* are the beginning and end of the computing window, *right* and $left$ the side and X_i and Y_j the h^2 channels considered for each side.

When S_{ide} is positive, it means that seizure onset may be on the right side, when negative it may be on the left. All the results are compared with the visual analysis of the neurologist.

Results

We computed the algorithms described in Methods on the 87 data files, for which side and seizure beginning was known.

With chosen electrodes, one can compute up to 28 different combinations. We compared results given by either use of all or only 10 couples of correlation signals chosen with the help of the specialist for their anatomical specificity. The method was applied to 4 time windows ([0,+20]s, [-10,+20]s, [-30,+30]s or [-150,+150]s where 0 represents the indicated time of seizure onset given by the expert) and to both sets of combinations (table 1).

Table 1: Lateralization of seizure onset on 87 seizures compared to neurologists' analysis, based on h^2 (non-linear regression analysis) in 4 different time windows (manual indication of seizure onset)

Nbre of Comb.	(0,+20)s	(-10, +20)s	(-30, +30)s	(-150, +150)s
10	78.2%	77.0%	77.0%	74.0%
28	82.8%	81.6%	78.2%	70.1%

Better results were obtained for the first window and h^2 signals computed in [3.5-30]Hz frequency band. Moreover, one can see that results are improved when all combinations of pairs of electrodes are considered, except for the [-150,+150]s window.

For the semi automatic lateralization, the detector has a sensibility detection close to 70%, so 30% of seizure onsets were manually set. For the 30% of seizures not detected, non-detection was explained either by artefacts or by a non significant increase of correlation. When applied to semi-automatically indicated seizure onsets time, the algorithm provides a good lateralization rate of 88,2% (table 2).

On figure 2 and figure 3, the result of lateralization algorithm on a sliding window moving from the beginning to the end of the file is presented. As shown in table 1, narrow windows around seizure onset have better lateralization sensibility. The main problem encountered with a too narrow window is that there are many ocular artefacts on inter-ictal segments of EEG and the correlation of channels containing such artefacts is always higher so that the risk of false lateralization increase. That is the reason we decided to chose a window size of 40 seconds with an overlap of 10 seconds.

Table 2: Comparison of lateralization results between a manual and a semi-automatic seizure beginning indication)

Nbre of Comb.	Manual indic. of seizure beg.	Semi-Auto. Indic. of seizure beg.
10	78.2%	87.3%
28	82.8%	88.2%

When comparing all the results obtained, three main patterns appear:

The first, presented in figure 2, shows that lateralization is good on all the length of the file. Around seizure onset, difference between left and right increase doing a large peak. What can be observed is that the increase arise few seconds before seizure onset time indicated by neurologists. That may be the sign that in fact seizure has already begun, what could be confirmed by a simultaneous SEEG recording.

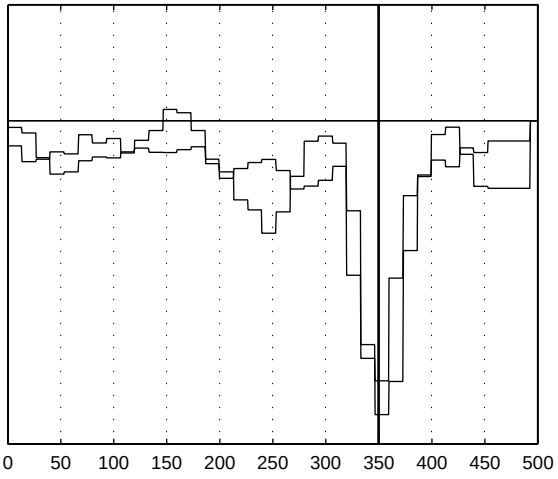

Figure 2: Example of lateralization evolution over time for two different seizures of the same patient. Beginning of seizure indicated by neurologists are represented by vertical lines (both at 350s and 350s). In this case lateralization is stable in time and considered as "good" relatively to neurologists indication even 300s before seizure

The second pattern, is shown on figure 3. Lateralization is false until few seconds before seizure occurs. Around seizure, lateralization is good and remains quite stable until the end of the seizure. As observed on figure 2, seizure onset time indicated by neurologists correspond to the local maximum value of the peak (respectively minimum if the seizure is left). What is outstanding on both cases shown is the reproducibility of the lateralization pattern, that may be explained by reproducibility of TLE seizure.

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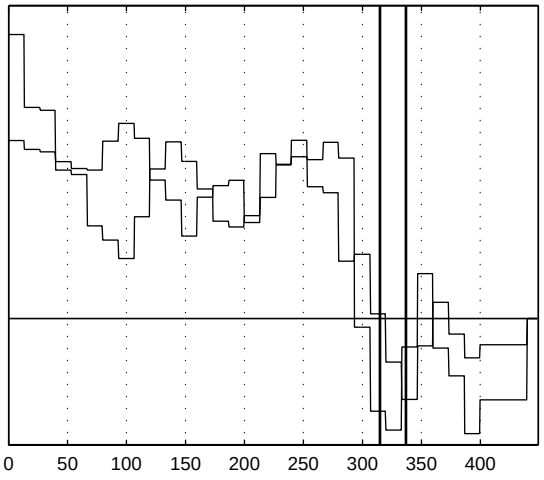

Figure 3: Example of lateralization evolution over time for two seizures of same patient. Beginning of seizure indicated by neurologists are represented by vertical lines (at 315s and 337s). In this case lateralization is stable in time and considered as "false" relatively to neurologists indication. Lateralization become "good" only few seconds before seizure onset is indicated by neurologist

The third pattern, is a false lateralization around seizure. In this case, generally, no peak can be seen and signal is never really lateralized. And S_{ide} coefficient vary around zero. If lateralization algorithm is applied to whole data files (450s or 500s around seizure onset time), the rate of good lateralization fall to 70%.

Discussion

One of the important thing that was pointed out in this paper, is that non-linear regression can be successfully applied to scalp EEG to realize different analysis. In several articles [12, 13], it was used on SEEG signal to point out epileptic neural networks or even seizure onset. To our knowledge, it is the first time that this method is used on surface EEG, whatever the application. So as, seizure onset lateralization computed on h^2 signals extracted from scalp EEG is very good (more than 80%), we ensured that even if scalp EEG is a recording of the activity produced by a large part of the brain, some informational data can be taken out of them.

When comparing manual indication of seizure onset to a semi-automatically one, we see an improvement of the lateralization results. That can be explained by the difference in the definition on a seizure onset between the neurologists and our detection algorithm. For the neurologists, the seizure onset is indicated by the first change in EEG signal (flattening, change in rhythm, ...) whereas for our algorithm it is when h^2 signal sufficiently increase on a minimum number of channels. Both information generally lead to the same time but some differences are observed, when seizure indication of the neurologists is not the beginning of theta rhythmicity or when it is too many muscle artefacts are present.

Using semi-automatic procedure (expert indication of the epileptic seizure if false detection occurs), we were able to correctly determine the side of the onset in about 88% of the studied EEG recordings. These results are obtained by comparing the non-linear correlation h^2 on windows automatically adapted to the length of the epileptic seizure. In fact the variation of good lateralization do not vary much whatever the length of computation window, the only important thing is to have at least 20s around the seizure onset, where correlations are higher.

Compared to other techniques, (analyse of interictal spikes [7] or analyse of MRI [14]), our technique has a better lateralization rate (more than 80% when using the good window). The main advantage of our technique is that it exploits video-EEG recording and that the result can be quite immediate after a seizure.

Conclusions

In this paper we introduced a new method based on scalp EEG signal that indicates the side of the seizure onset zone for TLE patients. The main idea is that non-linear correlation h^2 between EEG channels corresponding to the seizure onset side is higher than on the contra-lateral side.

This study demonstrates that the increase in correlation can indicate the side of seizure onset in a large amount of patients with TLE. The difference between manual and semi-automatic lateralization comes from the definition of seizure onset for neurologists, it is the first sign seen in EEG signals. Further works will investigate the relationship between changes in EEG signals during the transition to seizure and the increase of correlation between signals.

A critical point, that will be the subject of our future research, is the whole automatic detection of seizure onset time, with high sensibility and specificity but not obligatory with a high precision. Furthermore, for a clinical application we must take into account other information concerning the exact condition of seizure occurrences (degree of awakening, time past since last seizure, etc...) that might influence on correlation degree, even in pre-ictal states.

When these both problems will be solved this technique could be used online to produce a lateralization probability as soon as seizure is finished. It could be an appreciable time saving information for neurologists in their future analyses of the patients' seizures.

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