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Study of interhemispheric asymmetries in electroencephalographic signals by frequency analysis

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Abstract. This study provides a new method for the detection of interhemispheric asymmetries in patients with continuous video-electroencephalography (EEG) monitoring at Intensive Care Unit (ICU), using wavelet energy. We obtained the registration of EEG signals in 42 patients with different pathologies, and then we proceeded to perform signal processing using the Matlab program, we compared the abnormalities recorded in the report by the neurophysiologist, the images of each patient and the result of signals analysis with the Discrete Wavelet Transform (DWT). Conclusions: there exists correspondence between the abnormalities found in the processing of the signal with the clinical reports of findings in patients; according to previous conclusion, the methodology used can be a useful tool for diagnosis and early quantitative detection of interhemispheric asymmetries.

1. Introduction

One of the main characteristics in an ICU is the continuous monitoring of biological variables of patients, in order to diagnose and intervene early the different events that may jeopardize the patient's life or let sequelae; this way significantly decreases mortality and morbidity. For neuro intensive care unit (neuro-ICU) is a priority, moreover the monitoring of respiratory and hemodynamic variables, the determination of other parameters that help to evaluate, directly or indirectly, the functionality of the nervous system structures, and detect pathological processes before there is a change in the clinical examination [1]. The continuous video-electroencephalography (CEEG) in the neuro-ICU is a diagnostic tool that allows to find changes in brain function and to detect transient events that can be difficult to determine clinically. Its indications are: 1) detection of subclinical epileptic seizures, 2) characterization of paroxysmal episodes, 3) assessment of the level of consciousness, 4) monitoring the burst-suppression pattern in an induced coma, 5) detection of ischemia and 6) prognosis [2]. It has shown that the EEG/CEEG is the most sensitive diagnostic test to detect acute cerebral ischemia and EEG changes may occur in the first five minutes of the disease developing [3]; according to it, the EEG/CEEG should be considered, in the same way that advanced imaging techniques and neurological examination, as a tool for early diagnosis, prognosis, clinical management and crisis detection in patients with ischemic events in evolution [4].

The CEEG in the neuro-ICU uses electrodes placed on the scalp, in accordance with a location protocol (International 10-20 System), and the analysis of the resulting signals is done through several montages, being the foremost, the longitudinal bipolar, also known as "double banana"
montage because of its schematic representation to display the EEG signals [5, 6]. Its interpretation requires trained personnel, who evaluates qualitatively, the different patterns and variations of the EEG signals recorded in the last 12 to 24 hours, which means that, in spite of continuous monitoring, analysis is discretized to one or two moments of time, which can lead to a delayed diagnosis of diseases that require immediate intervention to minimize sequelae, as in acute ischemic events.

Likewise, the interpretation of the CEEG depends on the examiner, often the change is not noticed immediately, and there are not basal quantitative values to establish a better comparison before and after any event that patients present. The EEG diagnosis of an ischemic event is done by the expert, through the detection of interhemispheric asymmetries. An asymmetry occurs when the percentage difference in amplitude between two contralateral homologous regions is above 50%. Most often, the visual analysis is performed by the expert in a qualitative way, so the subtle variations in the level of asymmetry, which may have clinical implications, may not be detected. Due to the limitations of the qualitative analysis, it should be accompanied by quantitative variables, for compare the dynamic changes presented by the brain. For these reasons, in recent years, quantitative EEG (QEEG) monitoring has taken strength as support in diagnostic and therapeutic decisions [7, 8, 9, 10, 11].

The QEEG Analysis is based primarily on the time-frequency relation, is done by means of mathematical tools, such as Fast Fourier Transform (FFT) or Discrete Wavelet Transform (DWT), this has opened a field of interest in the analysis and interpretation of EEG, and its application to different topics: 1) detection of ischemic and post-ischemia epileptogenic areas. After a stroke, the area of the cortex surrounding the ischemic zone is responsible for the functional recovery of the patient; however it can become epileptogenic zone in patients after stroke. The analysis by the FFT and DWT has demonstrated change in the frequency bands, which allows identifying the abnormal area, and potentially epileptogenic zone [12, 13, 14, 15, 16, 17, 18]. 2) diagnosis and prediction in cerebral ischemia. It has used the spectrogram with FFT and an artificial neural network trained and evaluated, as effective methods for early prediction and monitoring of cerebral ischemia, as well as to monitor the effects of drugs in this conditions [19]. 3) other applications. FFT and DWT have been applied in other conditions such as the effect of antiepileptic medication [20], detection of the anesthesia levels [21], detection of patients with schizophrenia [22], detection and quantification of sleep states [23], and gender and personality differences [24].

In the case of the detection of interhemispheric asymmetries, as a marker of ischemia and severity of the same, it has used the fast Fourier transform and derived tools for spectral relations, which have shown correlation with prognosis [25, 26], these quantitative parameters permit to have a more objective point of comparison, for the proper monitoring of patients underwent to neurosurgical procedures or who are at risk of developing acute ischemic events like patients with subarachnoid hemorrhage (SAH) [14, 27], however these studies have been based on the Fourier transform, this quantitative method presents some limitations: in time-frequency analysis and as well as implementation of algorithms in real time, which can cause diagnostic errors. This study proposes a new quantitative method for the detection of interhemispheric asymmetries, using discrete wavelet transform.

2. Patients and Methods

2.1. Study Population
We obtained retrospectively the record by EEG of patients (n=19) hospitalized with suspected non-convulsive epileptic state. They were included for the selection, all records obtained consecutively, in the period July 2008 to July 2010. Inclusion criteria were: (1) age: 14 years old, (2) located in the Neurological Intensive Care Unit, (3) with mechanical ventilation, (4) interhemispheric asymmetry diagnosed by neurophysiologist, (5) neuroimaging with lesional area diagnosed by neuroradiologist. Exclusion criteria were: (1) convulsive epilepticus status, (2) abnormal movements, (3) continuous nystagmus, (4) continuous eye blinking, (5) frequent external artifact, (6) electrographic ictal activity
or epileptogenic irritant unilateral activity (7), hypoglycemia (<50 mg/dL) or severe hyperglycemia (>400 mg/dL).

The suspected diagnosis of nonconvulsive status epilepticus was made by the neurointensivist, taking into account clinical findings such as unexplained neurological deterioration, continuous blink, or a poor neurological recovery, after remove sedation. For the determination of interhemispheric asymmetry, was taken into account the opinion of the expert in the visual inspection of the records, regardless of quantitative measurements between contralateral homologous signals.

2.2. Control participants
The EEG records of 23 patients, with diagnostic suspicion of non-convulsive status epilepticus in the same period of study, were analyzed with same inclusion and exclusion criteria, except for the presence of interhemispheric asymmetry diagnosed by neurophysiologist. The results are shown in Table 1.

| Asymmetry Group | Control Group |
|-----------------|---------------|
| Mean            | Total         | Mean | Total |
| Age             | 45<sub>a</sub> | 35<sub>a</sub> |
| Gender          |               |      |       |
| Male            | 12            | 14   |
| Female          | 7             | 9    |
| Diagnosis       |               |      |       |
| Stroke          | 3             | 4    |
| SAH             | 5             | 4    |
| Neuroinfection  | 2             | 6    |
| Resection       | 4             | 2    |
| Head trauma     | 5             | 7    |

<sup>a</sup>p<0.05.
<sup>b</sup>Chi square: 0.023 (p=0.879)
<sup>c</sup>Chi square: 2,899 (p=0.575)

2.3. EEG Acquisition
Ag/AgCl electrodes were positioned on the scalp, according to the international 10-20 system, with impedances <5kΩ in all contacts. Analog-to-digital (AD) conversion was 200 Hz for all channels, using an 8-bit AD converter. The EEG was registered and observed using the Easy3 program (Cadwell Inc, USA), during the time ordered by the treating specialist, and it was discontinued when the study was completed or decided by the neurointensivist. It was used a bipolar longitudinal montage for the entire record, getting 18 channels: 8 left (FP1-F7, F7-T7, T7-P7, P7-O1, FP1-F3, F3-C3, C3-P3, P3-O1), 8 rights (FP2-F8, F8-T8, T8-P8, P8-O2, FP2-F4, F4-C4, C4-P4, P4-O1), and two central (FZ-CZ, CZ-PZ). They were distributed as is shown in figure 1.

2.4. EEG preprocessing
It was used a band pass filter (high-pass 1 Hz and low pass 70 Hz), with a 60 Hz notch filter. From each patient was selected, at least, one sample of five minutes artifact-free EEG recording, where the interhemispheric asymmetry was clearly evident, and was recorded in the channels which were shown the asymmetry. For control patients it was selected a sample of five continuous minutes artifact free. From all records were excluded those that presented unilateral epileptogenic irritative activity, that could affect the result for interhemispheric asymmetry detection. Each sample with 18 channels was converted to EDF format (European Data Format) and then to ASCII format, for analysis in MATLAB environment, with additional scripts developed.
2.5. EEG analysis

Each signal was processed in all parameters, taking epochs of 2, 5, 10, 20, 30, 60 and 300 seconds and then these results were compared. The following parameters were analyzed:

2.5.1 Average amplitude of the signal (V). For each signal and epoch were calculated maximum value (Xmax) and minimum (Xmin) in microvolts, calculating the average value obtained by the formula:

\[
V_i(j) = \frac{1}{N} \sum_{j=1}^{N} \left( \frac{|X_{max,i}(j)| + |X_{min,i}(j)|}{2} \right)
\]

\[
i = \frac{(2,5,10,20,30,60,300)\text{sec}}{\text{epoch}}
\]

\[
N = \frac{t}{i}
\]

Where \(t\) is duration in seconds of each signal.

2.5.2 Percentage difference in amplitude (%ΔV) and greater amplitude side. A quantitative calculation was performed of the potential differences of each of the eight channels on one side of the brain, with the contralateral homologous, using the following formula:

\[
\%ΔV_{reg} = \frac{V_{reg_{max}} - V_{reg_{min}}}{V_{reg_{max}}} \times 100
\]

Where \(reg\) are each of the 8 regions that are obtained by compare the contralateral sides: frontopolar-anterior temporal, anterior temporal-middle temporal, middle temporal-posterior temporal, posterior temporal-occipital, frontopolar-frontal, frontal-central, central-parietal and parietal-occipital. For this calculation we excluded channels FZ-CZ and CZ-PZ, because they do not lateralize.
2.5.3. Wavelet transform. The wavelet is a vanishing oscillating function that can help to characterize any elements of the signal in both time and frequency. A wavelet family $\psi_{s,\tau}$ is the set of elemental functions generated by scaling and translation of a unique mother wavelet $\psi(t)$:

$$\psi_{s,\tau}(t) = |s|^{-1/2} \psi \left( \frac{t - \tau}{s} \right) \quad (3)$$

Where $s, \tau \in \mathbb{R}$, $s \neq 0$, are the scale and translation parameters, respectively, and $t$ is the time.

The discrete wavelet transform (DWT) provides a non-redundant representation of the signal $f$ and its values constitute the coefficients in a wavelet series, $(f, \psi_{s,\tau}) = C_f(s, \tau)$. These wavelet coefficients provide full information in a simple way and a direct estimation of local energies at the different relevant scales.

$$C_f(s, \tau) = \sum_t f(t) \psi_{s,\tau}^{*}(t) \quad (4)$$

$$f(t) = \sum_s \sum_{\tau} C_f(s, \tau) \psi_{s,\tau}(t) \quad (5)$$

2.5.4. Wavelet Energy of Signal (EA, ED). We performed a multilevel decomposition in each signal, using the Wavelet Discrete Transform Daubechies (db10), after decomposition at four levels, the coefficients were obtained with the following resolution levels (frequency bands): 35-70 Hz (detail level 1, corresponding to the gamma frequency spectrum); 17-35 Hz (detail level 2, corresponding to frequencies in beta range), 8-17 Hz (detail level 3, corresponding to alpha components at a greater percentage and also to beta components), 4-8 Hz (detail level 4, corresponding to the theta frequency), and 1-4 Hz (approximation level 4, which corresponds to delta frequencies) [28]. The spectral analysis of different decomposition levels is shown in figure 2. To each resulting subsignal from this procedure, was calculated energy. For approximation subsignal $A$ at decomposition level $j$ and each $i$ seconds per epoch, its wavelet energy corresponds to:

$$E_{A_j,i} = \sum_{k=1}^{N} |Ca_{j,i}(k)|^2 \quad (6)$$

Where $Ca(k)$ is the value of each of the subsignal decomposition coefficients. For the detail of subsignal $D$ in the decomposition level $j$ and each $i$ seconds for epoch, we calculated wavelet energy corresponds to:

$$ED_{j,i} = \sum_{k=1}^{N} |Cd_{j,i}(k)|^2 \quad (7)$$

As for the average amplitude, $\bar{u}$ energy values are obtained for each channel at a decomposition level $j$, therefore the arithmetic mean of the energy with standard deviation was obtained as parameter.
Figure 2: Power spectrum of different subsignals obtained by a multiresolution analysis, using Wavelet discrete transform Daubechies 10. a. Subsignal at $A_4$ level. b. Subsignal at $D_4$ level. c. Subsignal at $D_3$ level.

2.5.5. Percentage difference in energy ($\%\Delta E$) and greater energy side. Analogous to the calculating the percentage difference in amplitude, we proceed to perform this wavelet energy percentage difference for each pair of homologous regions and contralateral obtaining, for each sample, eight values, corresponding to the eight regions previously described:

$$\%\Delta E_j(reg) = \frac{E_{j,reg M} - E_{j,reg m}}{E_{j,reg M}} \times 100$$  \hspace{1cm} (8)

For each energy comparison between contralateral homologous regions, it was calculated the higher energy side by a procedure similar to that used in calculating the greater amplitude side.

2.6. Statistical Analyses

Each of the five parameters calculated in selected samples were correlated and compared, discriminating them depending on case group (asymmetry) or control group (normal). SPSS® software was used to analyze information obtained from the calculated measures. We compared the average amplitude in each channel with its respective wavelet energy average in its different decomposition levels. We used the Spearman’s correlation coefficient (see equation 9) and was made the graph, approximating the dispersion curve to the best fit. It is expected that energy is proportional to the square of amplitude, so the best approach would be with a quadratic function. The comparison between the percentage difference in amplitude and the percentage difference in energy also was performed using the Spearman’s correlation coefficient. These results also were compared visually, by means of dispersion graphic, and with a linear approximation function.

Spearman’s correlation coefficient

$$\Gamma = \frac{\sigma_{XY}}{\sigma_X \times \sigma_Y}$$  \hspace{1cm} (9)
3. Results

A total of 19 patients with asymmetries (12 males, average age 44 years), and 23 without asymmetries (14 males, average age 35 years), with clinically suspected non-convulsive status epilepticus, were evaluated. The most common diagnoses in patients with asymmetry were traumatic head trauma and SAH. The most common diagnosis in patients without asymmetries was head trauma, followed by neuroinfection (see Table 1). The most common region for asymmetry was the left hemisphere (12 of 19 cases). Of the total cases and control patients were obtained 70 records of five minutes duration each, and were taken as the unit of analysis. Each patient had at least one record, but in some patients were obtained more than one artifact-free record.

Table 2. Measures of central tendency and dispersion for the percentage difference in amplitude comparing records with and without asymmetries

| EEG asymmetry by expert (%) | no | yes |
|-----------------------------|----|-----|
| Mean                        | 16.37 | 48.28 |
| Percentage difference in amplitude (%ΔV), epoch 10 sec. |   |     |
| Standard deviation          | 12.21 | 13.88 |
| Median                      | 13.37 | 48.62 |
| Percentile 25               | 6.67  | 40.02 |
| Percentile 75               | 24.06 | 57.82 |

3.1. Quantitative Asymmetry vs. asymmetry by Visual analysis

It is currently accepted definition of interhemispheric asymmetry as significant if the percentage of the difference in amplitudes is above 50%, however, a patient may have a clear interhemispheric asymmetry and an underlying pathological basis without having a difference over 50%. The analysis results in patients with interhemispheric asymmetries in EEG were diagnosed by neurophysiologist, then this results were compared with the percentages obtained using the parameter %ΔV, and shown in Table 2. As can be seen, the median of asymmetry value for this series is 48.6%, with values of 25th and 75th percentile between 40% and 57.8%, respectively. These results are consistent with what is accepted in literature, however it is important take into account that for QEEG analysis, are needed values above 35% to consider a possible asymmetry (mean 48%). Records without asymmetry, among which are parts some regions of case patients, has a median of 13.4%, with percentiles 25th and 75th between 6% and 24%, and the mean of this group without asymmetry was 16%, in normal records is possible to find differences in amplitude up to 30%. The summary by region is shown in figure 3.

Table 3. Correlation between the difference in amplitude and the difference in wavelet energy at its different decomposition levels.

| Difference in amplitude | Pearson Correlation | Difference energy A4 | Difference energy D4 | Difference energy D3 | Difference energy D2 |
|-------------------------|---------------------|-----------------------|----------------------|----------------------|----------------------|
|                         | Sig                 |                       |                      |                      |                      |
| N                       | 528                 | 528                   | 528                  | 528                  |

**Correlation is significant at the 0.01 level (2-tailed)
3.2. Difference in amplitude vs difference in wavelet energy

Having established the correspondence between the asymmetry visual assessment (qualitative), and asymmetry quantitative analysis, we proceeded to compare the amplitude, the side of greater amplitude, and the difference in amplitude with the respective energy values, difference in energy and the wavelet energy higher side. The results are shown in table 3 and figure 4. The best correlation is given between the difference in amplitude and the difference in energy at A4 level of decomposition (Pearson coefficient 0.929), this way we can extrapolate the difference in amplitude, as a marker for interhemispheric asymmetry to the difference in A4 energy taking into account a range of values as it is shown in Table 4. Doing the calculation of the difference in wavelet energy, the new value of asymmetry is 73%, with 25th percentile of 61%, and mean 70%. The importance using this relation is taking in advantage other characteristic of the wavelet transform, in relation with its time-frequency analysis. The polynomial approximation of these relation is shown in figure 5.

![Figure 3](image1)

**Figure 3.** Comparison between median of asymmetry percentages in accordance with control group (a) and case group (b). X-axis: percentage. Y-axis: eight regions of the scalp. Conventions. fpt: frontopolar-anterior temporal, tam: anterior temporal-middle temporal, tmp: middle temporal-posterior temporal, tpo: posterior temporal-occipital, fpf: frontopolar-frontal, fc: frontal-central, cp: central-parietal and po: parietal-occipital.

3.3. Correspondence in the greater amplitude side and greater energy. We used contingency tables, and a correlation between nominal variables using the kappa index; comparing the greater amplitude side in each of the examined regions, and 10 seconds epoch with the greater amplitude side obtained with each of the energy differences at diverse levels of decomposition (Table 5). Again, there is a better match between the amplitude and energy at A4 level of decomposition, with this transform is possible to work interpreting the signals in relation to their amplitude, and the calculation of asymmetry between contralateral homologous regions.

4. Discussion

When we realize the asymmetries analysis in EEG record, we have two possibilities of decision:
1. There is asymmetry for lower voltage in one hemisphere or zone.
2. There is asymmetry by a higher voltage in the other hemisphere or zone.

In most cases is easy to describe which of the two possibilities is correct, since an image showing an ischemia or infarction area in one hemisphere will support the diagnosis in the EEG, with the asymmetry; this is because to a lower voltage in the hemisphere or involved region. Otherwise, if we have a patient who does not have areas of ischemia or infarction by imaging, but he presents right temporal lobe epilepsy, then the displayed asymmetry will be caused by increasing voltage in the epileptogenic zone. However, when we have a patient with images that show areas of infarction in one hemisphere and additionally he is a seizure, it is necessary to analyze in detail the predominant frequencies in the record, and how these can be changed over time.
Figure 4. Correlation between difference in amplitude (X-axis) and difference in wavelet energy (Y-axis), according to their different levels of decomposition. a. A4 level, b. D4 level, c. D3 level, d. D2 level.

Table 4. Measures of central tendency and dispersion for the percentage difference in wavelet energy, by comparing records, with and without asymmetries

| Percentage difference in amplitude (%V) epoch 10 sec. | EEG asymmetry by expert (%) |
|------------------------------------------------------|-----------------------------|
|                                                      | no  | Yes |
| Mean                                                 | 29.52 | 70.28 |
| Standard deviation                                   | 20.05 | 15.99 |
| Median                                               | 26.96 | 72.76 |
| Percentile 25                                        | 12.45 | 61.16 |
| Percentile 75                                        | 44.06 | 81.22 |

There is a main limitation for asymmetries analysis because the expert cannot perform it continuously; this fact avoids having more objective parameters to compare the evolution of hours and days in patients who are hospitalized. An alternative would be to calculate the difference in signal amplitude, however this signal only is limited to values of potentials; the wavelet transform can be an indicator of asymmetry in voltage, and contribute with more signal characteristics allowing also be implemented in real time, since its computational algorithms are shorter than the FFT, and give more robust results than previous one. Wavelet transform is a tool that can adequately discriminate records with interhemispheric asymmetry of records without it, and thus it can be useful in diagnosis as well as following-up of monitored patients in the neuro-ICU with CEEG.
To implement the diagnosis, prognosis and treatment of patients under study by EEG video monitoring, the discrete wavelet transform could be a very interesting application. Among the patients under study by EEG video monitoring, there are cases with diagnosis of subarachnoid hemorrhage (blood vessel brain disease, which are broken by a weak artery wall and generates a mass effect that puts pressure on other brain structures), this disease has a mortality rate over 50%. It remains as a medium-term work, carrying out a research in patients with SAH and a prolonged EEG video monitoring.

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