Frequency evolution during tonic-clonic seizures[§]

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Abstract

By using the Short Time Fourier Transform, we analyzed the EEG frequency evolution during tonic-clonic seizures on 18 scalp recordings corresponding to 7 patients admitted for Video-EEG monitoring. This information was correlated with clinical findings observed in the video recordings. From the time-frequency plots, we recognized patterns related with brain activity even when embedded in a background of muscle artifacts. In 13/18 seizures we found a clear frequency dynamics characterized by an activity originally localized at about 8 Hz, later slowing down to about 1.5 Hz. In the remaining cases muscle artifacts hinder the disclosure of a clear frequency evolution. The clonic phases started when the main frequency slowed down to about 3 Hz.

We conclude that the Short Time Fourier Transform is very useful for a quantitative analysis of epileptic seizures, especially when muscle artifacts contaminate the recordings. We further conclude that the clonic phase starts as a response to brain activity that can be only established when brain oscillations are slow enough to be followed by the muscles.

1. Introduction

Since the first recordings in the late '20s, the electroencephalogram (EEG) has been one of the most extended and used tools in neurophysiology. An important application of EEGs is for the study of epileptic patients, in which deviations from the "normal" patterns help to classify epilepsies and eventually to localize the epileptic focus. About 30% of the epileptic patients do not respond to antiepileptic drugs (AEDs) and are therefore considered potential candidates for surgery (Kwan and Brodie, 2000; Hauser and Hesdorffer, 2001). As part of a comprehensive evaluation of these patients, spontaneous seizures obtained from long term Video-EEG recordings are analyzed. EEG activity is usually measured from the scalp but in those seizures where high muscle activity is involved, muscle artifacts rapidly confound their interpretation. This is the case of tonic-clonic seizures, in which the EEG analysis is usually confined to segments that either precede or follow the seizure activity, thus neglecting the true ictal phase. When information obtained from non-invasive techniques is not conclusive, patients may undergo implantation of intracranial electrodes. On the one hand, intracranial electrodes allow a better localization and minimize the effects of muscle artifacts, but on the other hand, their application requires a mayor surgery.

Although EEG recordings have been used for more than 70 years, their conventional analysis mostly relies on its visual inspection. However, with the introduction of digital computers in the storing and analysis of EEGs, quantitative methods of analysis have been developed. One mayor goal of these methods is to obtain more information from non-invasive techniques. Among them, the Fourier Transform or its time evolution, namely the Short Time Fourier Transform (STFT), have emerged as very powerful tools that allow a clear visualization of the periodicities of the signal (Dumermuth and Molinari, 1987; Lopes da Silva, 1993) . The Fourier representation is particularly useful when several frequencies are superimposed, thus being difficult to recognize them from a visual inspection of the data. In particular, it is the objective of this study to analyze from scalp recordings the frequency evolution during tonic-clonic seizures by using the STFT. Noteworthy, in most cases brain activity will be recognized even when lying in a background of high muscle activity and will be further correlated with clinical evidence obtained from the video analysis.

2. Methods

2.1. Subjects and recordings

Eighteen secondarily generalized tonic-clonic seizures (GTC) from seven epileptic patients were analyzed. These patients were admitted to the epilepsy monitoring unit with diagnosis of pharmacoresistant epilepsy and no other accompanying disorders (see Table 1 for clinical data). Antiepileptic drugs (AEDs) were gradually tapered after admission. Ictal electroclinical findings were compared with those obtained from interictal EEGs, MRIs, ictal and interictal SPECTs and psychological tests in order to identify, when possible, the anatomical focus of the seizures.

Scalp and sphenoidal electrodes with linked earlobes references were applied following the 10-20 international system. Each signal was digitized at 409.6 Hz through a 12 bit A/D converter and filtered with an "antialiasing" eight pole lowpass Bessel filter with a cutoff frequency of 50 Hz. Then, the signal was digitally filtered with a 1-50 Hz bandwidth filter and stored, after decimation, at 102.4 Hz on a PC hard drive. In order to study the effects of muscle artifacts in the scalp EEG during GTC seizures, for one additional patient (CB) we also analyzed three GTC seizures recorded simultaneously from scalp and intracranial electrodes. In the case of the intracranial electrodes, we analyzed the recordings obtained from an electrode placed in the right mesial temporal lobe. The scalp recording was measured bipolarly from the T4-T6 (right temporal) locations.

2.2. Data Analysis and Processing

Analysis of each event included one minute of EEG before the seizure onset and two minutes comprising the ictal and post-ictal phases. Seizure onset was defined electrographically as the first sustained change in the EEG clearly different from the background activity. Changes related with seizure onset comprised EEG attenuation (flattening), appearance of rhythmic activity, low frequency bursts and spike complexes. All 3 minutes were analyzed from the right central (C4) electrode. EEG findings were correlated with information obtained from the video recordings analyzing seizure semiology, onset of tonic and clonic phases, presence of muscular activity and other artifacts.

Frequency evolution was studied with the Short Time Fourier Transform (STFT; also called Windowed Fourier Transform; Cohen, 1995). It consists of applying the Fourier Transform to time-evolving data segments (windows) of a few seconds. Power spectra were estimated as the square of

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the Fourier Transform for each data segment. In order to improve the estimation, local averaging over nearby frequencies was done using a Bartlett-Priestley smoothing function (Priestley, 1993) and then each spectrum was normalized (the sum of the power over all frequencies equal to 1).

In figure 1, from top to bottom we show the power spectra of a seizure EEG recording (seizure #3 of patient LP) calculated with half overlapped windows of 20, 10, 5, 2.5 and 1.25 seconds width, respectively. As expected, larger windows are correlated with a higher frequency resolution but with a corresponding uncertainty in the time scale. On the other hand, short windows are well resolved on time but the frequencies look more spread and fluctuating due to its poor resolution.

For resolving the frequency evolution during tonic-clonic seizures half overlapped windows of 5 sec width were chosen as an optimal compromise between time and frequency resolution (time resolution = 2.5 sec; frequency resolution = 0.2 Hz).

3. Results

3.1. Muscle activity

Figure 2 shows a simultaneous intracranial and scalp EEG recording of a tonic-clonic seizure with their corresponding power spectra (seizure #1 of patient CB). Seizure started at second 60 with oral automatisms followed a few seconds later by a generalized tonic contraction. In the scalp and in the intracranial recordings, the power spectra of the EEG records show a pre-seizure activity that is distributed in frequencies less than 20 Hz. Both in the intracranial and in the scalp recordings, seizure onset is correlated with a flattening of the EEG lasting for about 3 seconds. In the intracranial recording, the EEG flattening is related with an increase of the frequency of the signal, distributed between 10 and 30 Hz. About five seconds after the starting of the seizure, a rhythmic activity with increasing amplitude appears, with its frequency decaying as the seizure evolves. In the time-frequency plot this is correlated with a well-localized activity (in comparison with the pre-seizure EEG and the initial EEG flattening) at about 9 Hz, later slowing down to 2 Hz at the ending of the seizure.

In the case of the scalp recording, a few seconds after the starting of the seizure muscle activity contaminates the EEG and it is not possible to recognize a rhythmic activity as the one seen in the intracranial recording. In the time-frequency plot, this muscle activity is correlated with the appearance of a widespread pattern involving frequencies up to 50 Hz. The fact that this pattern is only present in the scalp recording shows that it is mainly correlated (some non-localized EEG activity, such as the initial EEG flattening, could also contribute to it) with muscle activity, not measured in the intracranial EEG. This finding, i.e. the appearance of a widespread pattern only in the scalp recordings was common to the other two seizures of patient CB, where simultaneous scalp and intracranial recordings were analyzed.

3.2. Frequency evolution

Figure 3 shows seizure #1 of patient LP and its corresponding power spectra. Seizure started at second 80 with oral authmatisms follwed 20 seconds later by a generalized tonic contraction. In the EEG, the onset of the seizure is correlated with a low frequency burst, with high frequency activity superposed to it. About ten seconds after the starting of the seizure, a rhythmic activity appears. As in the case of the intracranial recording of figure 2, this rhythmic activity has

increasing amplitude and its main frequency slows down as the seizure evolves. In the time-frequency plot, this is correlated with the localized activity at 10 Hz clearly differentiated from the widespread frequency composition of the pre-ictal stage. This activity progressively slows down to 1 Hz at the seizure end. As observed in the video recording, the clonic phase started about 60 sec after the beginning of the seizure and is correlated with a localized activity at 3 Hz in the frequency domain. Muscle artifacts that somehow obscure the EEG recording, especially after second 115, are also identifiable in the time-frequency plot as a widespread pattern going up to frequencies larger than 30 Hz. However, due to their widespread appearance in contrast to the localized time-frequency pattern of the brain activity they do not obscure the described pattern. Again we cannot exclude the possibility that other EEG activity non-localized in frequency is masked by the muscle activity.

Figure 4 shows seizure #2 of patient JI, in which a localized time-frequency distribution correlated with real brain activity was not distinguishable due to muscle artifacts. Note that a few seconds after the starting of the seizure muscle activity obscures the EEG recording and it correlates with the widespread high frequency activity seen in the time-frequency plot. The only localized activity appears at about second 140 with a frequency of 2-3 Hz and it is correlated with the development of the clonic phase.

As shown in figure 4, in 5 of the 18 seizures (seizure #2 and #4 of patient FT, seizures #1 and #2 of JI, seizure #1 of AS) it was not possible to identify a clear frequency evolution due to muscle artifacts. In the remaining 13 cases, a frequency evolution like the one described in figure 3 was observed. Between 0 to 27 sec (mean: 13 sec) after the starting of the seizure the broadband frequency activity of the pre-seizure stage was replaced by a localized activity at 6.5-10 Hz (mean: 7.9 Hz) slowing down to 1-2 Hz (mean: 1.4 Hz) at seizure ending. The average rate of decay was of 0.127Hz/sec (range: 0.090Hz/sec-0.212Hz/sec). The clonic phase started between 25-66 sec (mean: 52 sec) after the beginning of the seizure and was correlated with a localized frequency activity at 2.5-4 Hz (mean: 3.16 Hz).

4. Discussion

4.1. Contamination of muscle activity

The Short Time Fourier Transform provides an attractive approach for visualizing the frequency evolution of scalp EEG activity during seizures. It is remarkable that in a single plot we could display the relevant information contained in minutes of an EEG recording. Furthermore, muscle activity characteristic of the tonic phase was identified as a widespread pattern in the time-frequency plots, therefore being possible to distinguish it from brain activity localized in frequency.

The presence of muscle activity in scalp recordings often limits the analysis of tonic-clonic seizures to the onset and post-ictal stages (and in some cases, even the seizure onset is obscured by muscle activity). However, interesting information could take place during the seizure itself. Blume and coworkers (Blume et al, 1998) reported the importance of "late seizure findings" (i.e. at least 5 sec after seizure starting) when no clear information was obtained from the seizure onset. This is in agreement with our findings. Note that we found the frequency dynamics starting up to 27 sec after the seizure onset (seizure #1 of patient IV). This information remains usually out of sight in the conventional EEG visual analysis.

Another approach to avoid muscle activity would be to use low pass filters. However, since the EEG and EMG have overlapping frequency distributions, it is impossible to determine a clear-cut in the frequency domain between EEG and EMG activity. Despite these problems, Gotman et al. (1981) successfully showed the utility of low pass filtering for visualizing relevant information difficult to observe in the non-filtered signals. Nevertheless, they also reported that it was not possible to find a unique and universal procedure for separating EEG and EMG activities from scalp seizure recordings. In this line of results, Akay et al. (1999) reported the difficulty of a separation between EEG and facial EMG activity using "matching pursuit Wavelets". We remark that our approach is also not able to separate between EMG and EEG. However, it helps to visualize the latter one even when lying in a background of muscle activity. In this respect, real brain activity was recognized as localized and time evolving patterns in the time-frequency plots, in contrast to the widespread "noisy" patterns of mucle artifacts.

4.2. Frequency dynamics

In 5/18 seizures we did not find a clear frequency dynamics. With the present data and method of analysis it is difficult to discern if this dynamics was not present or if muscle activity hide it. In the remaining 13/18 cases, we found a frequency evolution specific to tonic-clonic seizures. It was characterized by a localized activity at 6.5-10 Hz later slowing down to 1-2 Hz at the seizure offset, with an average rate of decay of 0.127 Hz/sec. As observed in the video recordings, the clonic phase started at a frequency between 2.5 – 4 Hz. Based upon these findings, we conclude that low frequency discharges that are correlated with the clonic contractions appear as a slowing of the high frequency activity that dominates at the beginning of the seizure. Therefore, the muscular contractions of the clonic phase are a response to brain activity that can only be established when brain oscillations are slow enough to be followed by the muscles. In some cases, generalized tremors were seen following the tonic phase and before the clonic contractions took place. The frequency of these tremors was always in between the ones of the tonic and clonic phases, thus being an intermediate muscle response to the frequency dynamics established during tonic-clonic seizures.

These results further extend our previous findings showing a predominance of alpha and theta rhythms during tonic-clonic seizures, with a later increase of the activity of the delta band correlated with the clonic contractions (Quian Quiroga et al, 1997). Noteworthy, a similar frequency decrease was reported after increases of $GABA_B$ inhibition in a thalamic model of spindle oscillations (Wang et al, 1995; Golomb et al, 1996). These findings are also in agreement with patterns seen in in-vitro ferret thalamic slice preparations (von Krosigk et al, 1993).

Gastaut and Broughton (1972) analyzed a tonic-clonic seizure of a patient treated with curare. In agreement with our results, they described a 10 Hz "recruiting rhythm" during the tonic phase of the seizure, and as seizure lasted they observed a progressive increase of the activity of lower frequencies (5-6 Hz). More recently, Blume and coworkers (1984) analyzed the scalp EEG frequency content in a large database of electrographic partial seizures. They reported that most seizures begun with activity in the delta or theta bands. These frequencies either increased or decreased in the earlier stages of the seizures, a decrease being more likely in the later stages. The fact that in our study we only included seizures with secondarily tonic-clonic generalization is most likely to explain the differences between the unique and stereotyped dynamics we found and the more variable behavior they described. Moreover, the lack of tonic and clonic activities and even of

clinical manifestations in (at least) some of the seizures studied by them explain why these authors could visualize the frequency content from ictal scalp EEGs with no reported interference from muscle artifacts.

The problem of muscle contamination is minimized with the use of intracranial electrodes. However, since these are applied only in some particular cases they are much less common than scalp recordings. In mesial temporal lobe seizures studied from intracranial recordings, King and Spencer (1995) reported a typical pattern of rhythmic discharges of about 13 Hz with a decrease in frequency when it was manifested in any propagated site. Our results extend these findings by showing the same frequency dynamics from scalp recordings and also by correlating it with clinical findings (e.g. starting of the clonic phase) as observed from the video recordings.

For the objective of this work, we consider the time-frequency resolution reached with the Short Time Fourier Transform to be sufficient. However, in those cases where more resolution is needed, the Wavelet Transform, a new method of time-frequency analysis, gives an excellent resolution for all frequency ranges, therefore being an optimal tool for the analysis of data in which time and frequency resolution are critical (see Chui, 1992 for a theoretical background and Quian Quiroga and Schurmann, 1999; Blanco et al, 1998 for applications of Wavelets to EEGs). We should also mention that further quantifications of the time-frequency patterns, such as the band relative power studied in (Quian Quiroga et al, 1997), Shannon (Blanco et al, 1998) or relative (Quian Quiroga et al, 2000) entropies are candidates to give promising results in the study of epileptic seizures.

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Table 1: Clinical data of the patients studied

Patient	Age (years)	Sex	# of seizures	Ictal foci	Antiepileptic Drugs
CS	22	F	2	Right Temp.	VGB, CZP
LP	39	F	3	Left Temp.	CBZ, CZP
DLB	24	M	2	Bitemp.	LTG, OXCBZ, KBL
AS	49	M	4	Left Temp.	VGB, LZP, GBP
IV	22	F	1	Left Temp.	VGB, VPA, AZT
FT	6	F	4	Non local.	CBZ, VPA
JI	51	M	2	Non local.	CBZ, PB
CB	41	M	3	Right Temp.	CBZ, TPM

Abbreviations: LTG, lamotrigine; OXCBZ, oxcarbazepine; KBL, clobazan; VGB, vigabatrin; CZP, clonazepan; CBZ, carbamazepine; LZP, lorazepan; GBP, gabapentin; VPA, valproic acid; TPM: Topiramate.

Figure legends:

Figure 1: Power spectra of a scalp seizure EEG (seizure #3 of patient LP) calculated with different window sizes. Seizure starts at second 84 and ends at second 170. Note how with shorter windows the power spectrum is more resolved in time but with a corresponding decrease of the frequency resolution.

Figure 2: Simultaneous intracranial (A; right mesial temporal lobe) and scalp (B; T4-T6) EEG recordings of a tonic-clonic seizure (seizure #1 of patient CB) with their corresponding power spectra. Note the widespread frequency pattern appearing during the seizure in the scalp recording due to muscle artifacts. As expected, this pattern is not present in the intracranial recording. On the y-axis EEG activity in µV.

Figure 3: Scalp EEG recording from the C4 channel (A) during a tonic-clonic seizure (seizure #1 of patient LP) and its corresponding power spectra (B). Note the frequency evolution during the seizure with an initial localization at 10 Hz later slowing down to about 1 Hz. Clonic contractions start when the dominant frequency is 3 Hz. On the y-axis EEG activity in µV.

Figure 4: Same as the previous figure for seizure #2 of patient JI, in which a frequency evolution is not distinguishable due to muscle contamination.

A

Intracranial EEG

45 sec
Seizure start
200μ V | 2 sec
75 sec
105 sec
Seizure end

f (Hz)

Seizure start   Seizure end

B

Scalp EEG

45 sec
Seizure start
100μ V | 2 sec
75 sec
105 sec
Seizure end

f (Hz)

Seizure start   Seizure end

Time (sec)

A

200µ V | 2 sec

Seizure start

30 sec
60 sec
90 sec
120 sec
150 sec
180 sec

EEG

Seizure end

B

Seizure start

Seizure end

f (Hz)

30

25

20

15

10

5

0

0   20   40   60   80   100   120   140   160   180

Time (sec)