Automatic identification of Slow Biphasic Complexes in EEG: an effective tool to detect Encephalitis

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Abstract

Objective. The presence of slow biphasic complexes in EEG was found to be associated to different neural diseases, in particular inflammatory. This paper proposes a method to identify automatically the complexes and provides preliminary tests on paediatric patients with encephalitis. *Approach.* A prototype waveform was computed aligning and averaging complexes manually identified during years of investigation. A wide range of amplitudes and durations was noticed. The proposed automatic method is based on the cross-correlation of the tested EEG with scaled versions of the prototype waveform. The waves with high correlation with the prototype are identified as complexes if their amplitude and duration are reasonable and if they do not appear as pseudo-periodic oscillations. *Main results*. The algorithm was tested on a dataset of 128 EEGs from healthy controls and patients (for which the follow-up was also available). Experts assigned to each trace a severity score with 5 levels considering both electrophysiological and clinical manifestations. The number and amplitude of complexes are markers of encephalitis, they show statistically significant differences across EEGs with different severity scores and correlate with the condition of patients during the follow-up (median correlation about 80%). *Significance.* Inflammatory brain pathologies can have serious sequelae. Quickness of diagnosis and targeted therapeutic interventions are essential to avoid or limit the damages. The proposed automated method is feasible for the fast, accurate and non-invasive diagnosis of encephalitis and the follow-up of patients.

Abbreviations

CNS	central nervous system
CSF	cerebrospinal fluid
EEG	electroencephalogram
FFT	fast Fourier transform
HIV	Human Immunodeficiency Virus
ISI	inter-spike interval
RMS	root mean square
SBC	slow biphasic complex

Introduction

Encephalitis is an inflammatory process of cerebral parenchyma associated with neurological dysfunctions [1][2]. It can have an acute, subacute or chronic course caused by different processes, such as infectious diseases, immune or vascular disorders and cancer, in some cases [3]. The most common encephalitis with acute manifestations are the infectious, epidemic or sporadic, and dysimmune. Incidence in children is estimated at about 1 out of 10,000 [4]. Symptoms are generally non-specific and, in more than 50% of cases, the etiologic cause is not identified [4]. At the diagnosis, the following clinical criteria should be considered to assess the suspect of an inflammatory pathology of the cerebral nervous system (CNS) [4]: 1) cerebral or altered state of consciousness (major indicator); 2) fever, focal neurological deficits, seizures, abnormalities in neuroimaging and/or in the electroencephalogram (EEG), cerebrospinal fluid (CSF) pleiocytosis (minor features).

The effective treatment of encephalitis requires a rapid assessment of basic vital functions, serological and instrumental examinations. Emergency therapy is predominantly empirical and in association with antiviral drugs, antibiotics and steroids. Due to the multiple aetiologies, a general prognosis assessment is difficult. However, in the case of encephalitis by herpes simplex, which is the main etiologic agent, the lethal rate is in the range 5-20% (70% if not treated with acyclovir [5]).

The EEG may play a key role in the diagnosis and follow-up of patients with different encephalopathies [6][7][8]. Indeed, it is a well-established, safe, economical, easy-to-use and non-invasive technique which provides detailed information on the state of the brain. It found relevant results in the study of encephalitis [2][4][9][10][11][12][13]. In particular, we are interested in the presence of waveforms with a similar shape, known as slow biphasic complexes (SBC), which were observed in few studies in the EEG of patients with inflammatory processes of the CNS [14][15][16][17][18] and, in particular, with severe encephalitis [19]. They were characterized by the following properties [16]: 1) amplitude from about 50 to 200 μV; 2) duration of about 500 ms; 3) stereotypes with two similar waves with inverted polarity (i.e., a biphasic waveform); 4) similar waveforms are repeated, but they are sporadic, not periodic; 5) they can be either focal or generalized. We also found that they are more common during hyperventilation and in waking than during sleeping (not published observations). Moreover, low amplitude waveforms tend to appear at a higher frequency, but with a shorter duration.

Clinical evidence suggests that the onset of SBCs in EEG could be a marker of encephalitis and the number and amplitude of the complexes could be related to the severity of the pathology.

However, the identification of SBCs has been conducted until now by visual inspection by expert neurologists and no quantitative investigation of the relation between SBCs and severity of encephalitis has been documented. Notice also that it is simpler to identify the complexes in desynchronized background activity, than during pathologic slow activity, with bandwidth similar to that of the SBCs. Thus, subjective identification could be affected by a bias. In order to get an objective and quantitative evaluation, we propose here an automated algorithm able to identify the SBCs and a post-processing which quantifies the results (in terms of number of identified SBCs, their amplitude distribution, rate of appearance, spatial distribution, etc.). The correlation between the outputs of the algorithm and the severity of the pathology is then tested in different patients and during the follow-up.

Methods

Algorithm

Pre-processing

EEG data were pre-processed using a band-pass filter with cut-off frequencies at 0.1 and 30 Hz (combination of low- and high-pass filters, Chebyshev Type II filter of order 3 and 5, respectively, used in both directions to remove the phase). No other processing (e.g., artefact removal) was employed, so that all data within the bandwidth of interest was included.

Properties of complexes

Our routine investigation of EEG (during decades of activity of A.B. and G.C.) allowed to identify thousands of biphasic complexes in patients with different inflammatory chronic or acute pathologies, including encephalitis, Human Immunodeficiency Virus (HIV), multiple sclerosis and Rasmussen's syndrome. The prototype waveform shown in Figure 1A was found to reasonably fit experimental data. However, different amplitudes were found. Specifically, important complexes emerged from the background EEG activity, so that their amplitude was scaled with the root mean square (RMS) value of the investigated channel. Furthermore, differential signals were considered, so that the waveform of the biphasic complex could be also reversed. Moreover, different durations could be found, usually with larger amplitudes associated also to longer durations, so that the waveforms of different complexes appeared to be quite similar, but with different scaling (in both amplitude and time directions).

Complexes are usually found separated from each other: repetitive, pseudo-periodic activity is usually not related to SBCs.

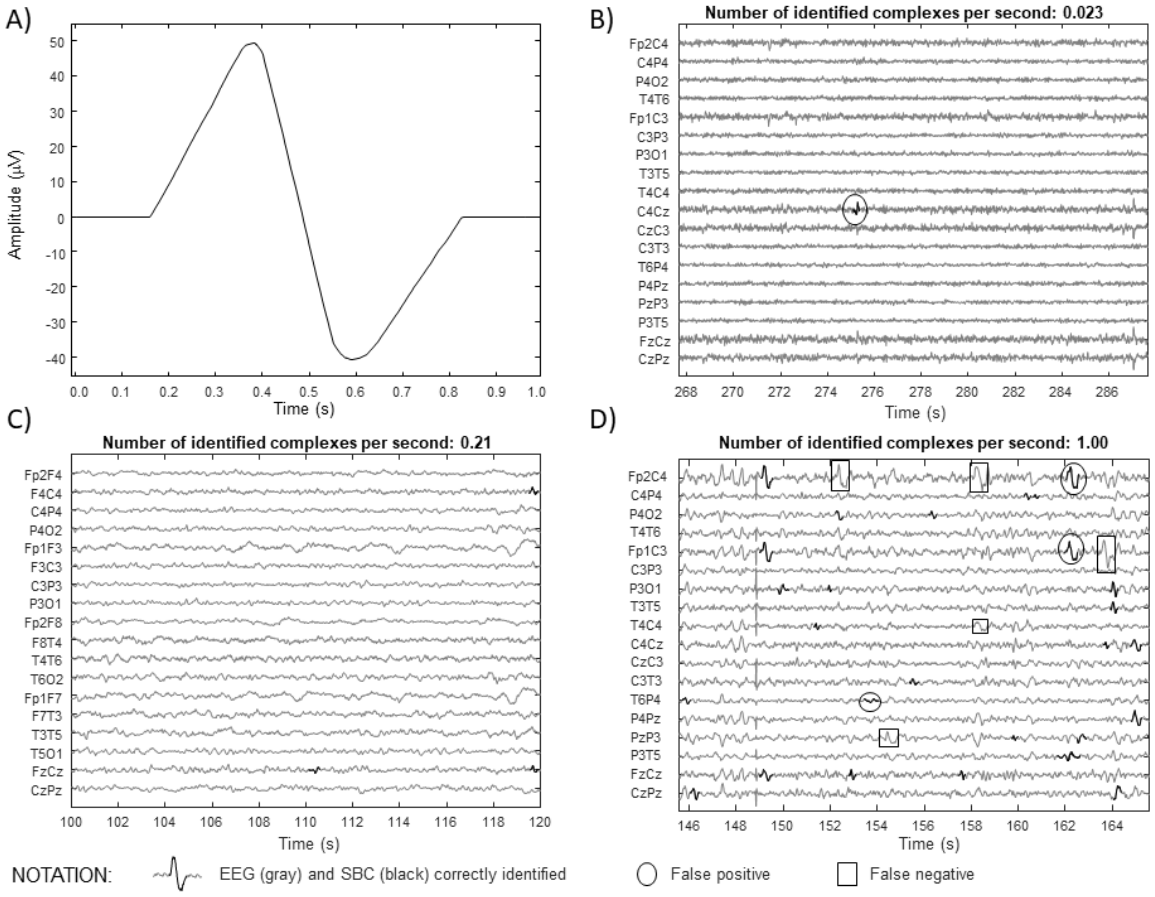

Figure 1. A) Prototype function representing a stereotyped slow biphasic complex (SBC). B) Example of a portion of EEG from a normal control (with the indication of the number of waveforms similar to a SBC identified by the automated algorithm). C) Portion of EEG from a patient with mild manifestations of encephalitis. D) Portion of EEG from a patient with serious manifestations of encephalitis.

Automated detection

Given the qualitative properties of the biphasic complexes discussed above, a set of match filters was used to identify them. Specifically, the algorithm was based on the following steps.

1. Different time scales of the prototype waveform were considered (specifically, 10 scales linearly distributed between 0.25 and 3 were applied to the prototype shown in Figure 1A).
2. The normalized cross-correlation of the EEG (from each channel) and the scaled waveform was computed

$$C(t) = \frac{\int x(\tau) w(t+\tau) d\tau}{\|x\|_2 \|w\|_2} \quad (1)$$

where *t* indicates the time variable, *x(t)* is the EEG of the considered channel, *w(t)* is the scaled prototype waveform and $\|\cdot\|_2$ is the RMS of the argument. Notice that the integral in the numerator of (1) is used as a general definition of cross-correlation, but, as data are sampled, it is numerically implemented as a finite sum. Due to the normalization, the above expression can take values between -1 (perfect match with the reversed waveform, i.e., - *w(t)*) and 1 (perfect match with the waveform). A perfect match with the scaled waveform cannot be expected due to the following problems: the prototype waveform is only a simulated stereotype of the biphasic complex, the number of considered scales is limited and noise is present (e.g., artefacts, electronic noise and interferences from external or bioelectric sources). Thus, a threshold at 90% (selected based on fine tuning on a subset of data) was considered to accommodate possible mismatches. The threshold was compared to the absolute value of the normalized cross-correlation (the absolute value was considered to include waveforms which were similar to either the prototype or its reverse).

3. The amplitudes of the waveforms identified in the previous step were investigated. Only those waveforms with an amplitude comparable to that of the channel were selected as complexes. Specifically, the envelope of the EEG in the investigated channel was computed (the envelope was defined as the absolute value of the EEG low-pass filtered with cut-off at 1 Hz, using a Chebyshev Type II filter of order 6, run in both directions to remove the phase). The cumulative distribution of the envelope was then estimated. The minimum amplitude of a complex corresponded to the 20% level of such a distribution, the maximum was the 99% level multiplied by 1.1. These thresholds were found to be stable to possible amplitude outliers (i.e., potentials with large amplitude probably related to artefacts and others with low amplitudes reflecting noisy oscillations). Moreover, they allowed to adapt the selection of the complexes to the amplitude distribution of the investigated channels.

The algorithm was implemented in MATLAB (Inc., Natick, Massachusetts, USA, ver. 2015a, interpreted single core implementation). The main task is measuring the cross-correlation, which was computed efficiently estimating all terms by convolution operations (implemented in MATLAB by using the Fast Fourier Transform – FFT – algorithm, thus with logarithmic cost). For example, the time varying energy of the signal (whose square root is in the denominator of equation (1)) was computed on the support of the translated prototype waveform by a convolution of the squared signal with a rectangular window. When run on an

average personal computer (with Intel® Core i7-2630QM, Quad-Core, clock frequency of 2 GHz, 6 GB of RAM and 64 bits operating system), the processing took about 1 s for a minute of data (however, consider that the computational cost changes in dependence of the data: specifically, it increases for data including many complexes and, in such a case, it could be about 2-3 s for one minute of processed data).

Examples of EEG data and identified complexes are shown in Figure 1B-D. Notice that a few false positive or negative were found by the experts who reviewed the shown portions of data.

Post-processing

Sometimes, waveforms with shapes similar to two scaled prototypes were selected twice. Thus, after the identification of the complexes, they were scanned to remove possible spurious selections.

Once selected the most probable complexes by the procedure detailed above, a final check was considered to remove waveforms with too large amplitude (probably reflecting an artefact) or too close to other complexes (indicating repeated discharges, usually found in periodic rhythms, which are not SBCs). The barycentre of each waveform was identified (referred to as the time of appearance of the SBC, in the following) and also its temporal duration, defined as twice the delay between its maximum and minimum. The distribution of RMS amplitudes of the waveforms identified in each channel was then estimated (integrating in their temporal supports); the waveforms with amplitude exceeding the mean plus three times the standard deviation of such an amplitude distribution were excluded as outliers. Moreover, the RMS of the identified complexes was computed in their temporal supports and in a time interval extended of 0.5 s (starting 250 ms before and ending 250 ms after the temporal support of the waveform). The ratio between the two RMSs was imposed to be larger than 1.1 for a complex to be retained (in this way, the complex was imposed to emerge from the background activity and waveforms involved in pseudo-periodic discharges were excluded).

Experimental signals

A retrospective study was conducted on EEG data acquired from 10 paediatric patients with a clinical condition compatible with the diagnosis of encephalitis (age 2-14 years; 5 males and 5 females) and 10 control subjects (age 1-15 years; 5 males and 5 females).
A consent for the examination and data processing was obtained from the parents of each participant. Spontaneous EEG was acquired by the Micromed system (with Intel® Core™2 Q8400, Quad-Core, clock frequency of 2.66 GHz, 3 GB of RAM and 32 bits operating system; band-pass filter with bandwidth 0.5-70 Hz, sample rate of 256 Hz).

The selected patients were not involved in ischemic, hypertensive and degenerative encephalopathy. In most cases, there was no familiarity and remote pathological history was predominantly negative. The main diagnosis was that of encephalitis and the aetiology was unknown in 6 cases out of 10 patients. Hyperthermia was the most common symptom present at onset. Alterations of the state of consciousness occurred in 9 cases. Disseminated lesions were found in the magnetic resonance images (MRI) and focal lesions were identified in computerized tomographies (CT).

Patients were monitored for a long period (from a few months to about 3 years, for 2 patients with severe neurological sequelae; hospitalization days were 22.3 on average) and showed different severity of the pathology during the follow-up.

The number of recorded differential channels was either 10 or 18. The choice of the correct EEG headset depended on the age of the patient (and dimension of the head) at the moment of investigation. The EEG headset with a reduced number of electrodes was also used in some subsequent non-diagnostic serial controls (the retrospective nature of the study did not allow to evaluate EEG acquisitions in standard conditions). In total, 128 EEGs were recorded. Specifically, 46 and 82 EEGs included 10 and 18 channels, respectively.

Each EEG was associated to a severity score (summarized by the following discrete scale) indicating the condition of the patient: 0 indicated normality; 1 to 4 reflected mild, moderate, severe and serious pathology, respectively; NC (not classified) was given to unmanageable EEG traces. The EEGs recorded from normal subjects (either controls or patients in a period in which they showed no sign of the pathology) were 22, those related to pathological manifestations were 29, 25, 22 and 20 for mild, moderate, severe and serious illnesses, respectively; 10 EEG were not manageable.

Statistical analysis

We tested the hypothesis that the following indexes (normalized dividing by the number of channels and the duration of the EEG) provide statistically significant information on the severity score given to the EEG: the number of identified SBCs, their number in frontal channels, their total amplitude in either all channels or the frontal ones. Kruskal-Wallis test was applied to check for a significant effect of the severity score. Wilkoxon signed rank method was applied as post-hoc test for pairwise comparisons, to check for significant ($p<0.05$) or highly significant ($p<0.01$) differences.

Results

Introduction

Some outcomes of the processing of our dataset are shown in Figures 2-6. Preliminary indications are first given, showing examples of EEG traces, identified complexes and a few properties which could be extracted by post-processing the output of the algorithm, e.g., the frequency of SBC appearance and the spatial distribution (Figure 2). The possibility of deepening the study of specific SBCs by an advanced post-processing is shown in Figure 3: considering again a specific EEG trace, similar SBCs are clustered, allowing to study their specific temporal occurrence, average shape and spatial distribution. All EEG traces corresponding to same severity score are pooled together in Figures 4 and 5, showing the average spatial distribution and the occurrences or amplitude of SBCs, respectively. Finally, Figure 6 shows the correlation between severity score and SBC occurrence/amplitude for each patient, indicating the potential usefulness of the automated method in the follow-up.

Examples of complexes identified in different subjects

Figure 2 shows two examples of processing, in the case of patients with either a normal condition or a serious manifestation of the pathology. Two cases with low number of channels are considered, showing, in the upper panels, portions of EEG data in the montage usually used for clinical investigation (notice that 12 differential channels are shown, but two couples are equivalent, i.e., C4T4 and T4C4, and C3T3, which is repeated twice; SBCs identified on those equivalent channels were shown only once). Sporadic waveforms are indicated by the algorithm as similar to SBC even in normal conditions. These are biphasic waveforms that show by chance a similarity with the shape of the SBC and pass the selection criteria. However, the rate of identified waveforms is small (about 0.16 per s), the distribution of inter-pulse interval (IPI; i.e., the time delay between successive appearance of the waveform) shows that their occurrence is sporadic and their amplitude is quite small and variable among different sources. The spatial distribution is random. On the contrary, the SBCs identified from the EEG recorded from the patient with serious manifestations of encephalitis are more frequent (about 0.8 SBCs per s). Moreover, they show an IPI distribution which has a peak for delays lower than about 1 s. The amplitude distribution is unimodal, with a peak at about 60 μV. Finally, there is a clear spatial distribution, as most complexes were identified in the frontal region.

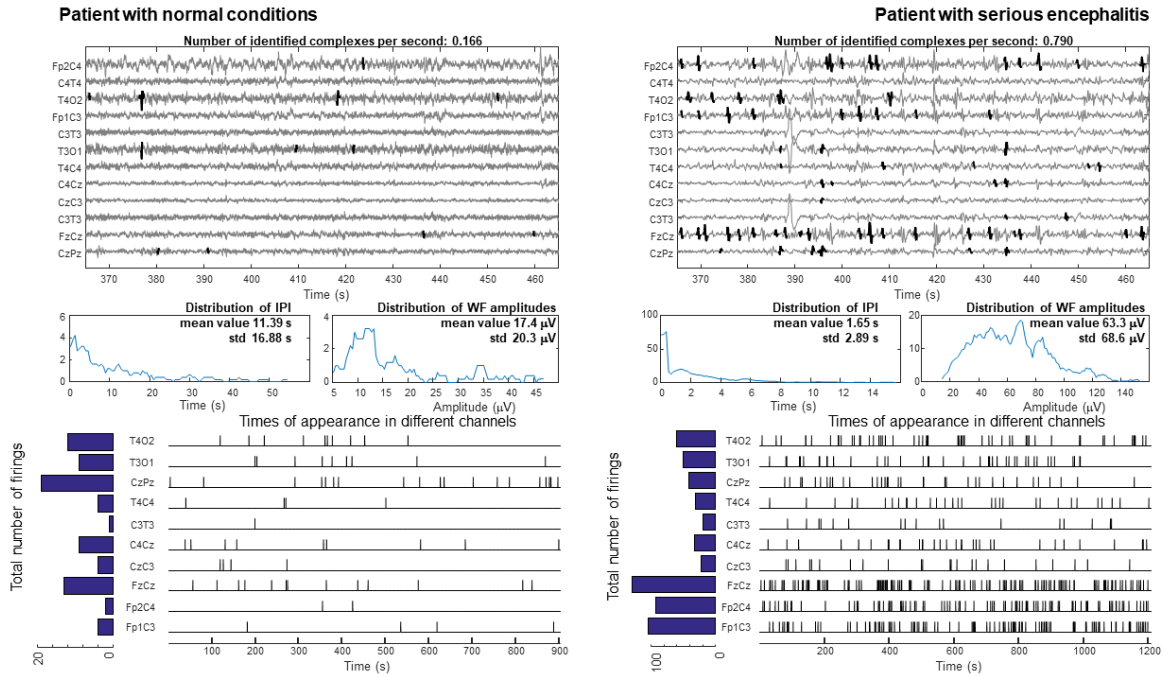

Figure 2. Investigation of complexes in patients with different conditions: normal condition (left) and serious manifestations of encephalitis (right). A portion of EEG is shown, with indication of the SBCs identified by the algorithm (SBCs are shown only once for repeated channels, i.e., C3T3 and T4C4/C4T4). The distributions of the inter-pulse interval (IPI) and of the amplitude of the identified waveforms (WF) are also shown. Finally, the instants in which SBCs were identified are shown for each channel (ordering the channels with decreasing distance from the frontal region).

Thus, the output of the algorithm appears to be more structured in the case of the EEG from the patient with serious illness, clearly indicating that the identification of the complexes is not due to chance (on the contrary, as mentioned above, waveforms identified in data from the patient in normal conditions show a random, not consistent appearance, suggesting that they were similar to SBC only by chance).

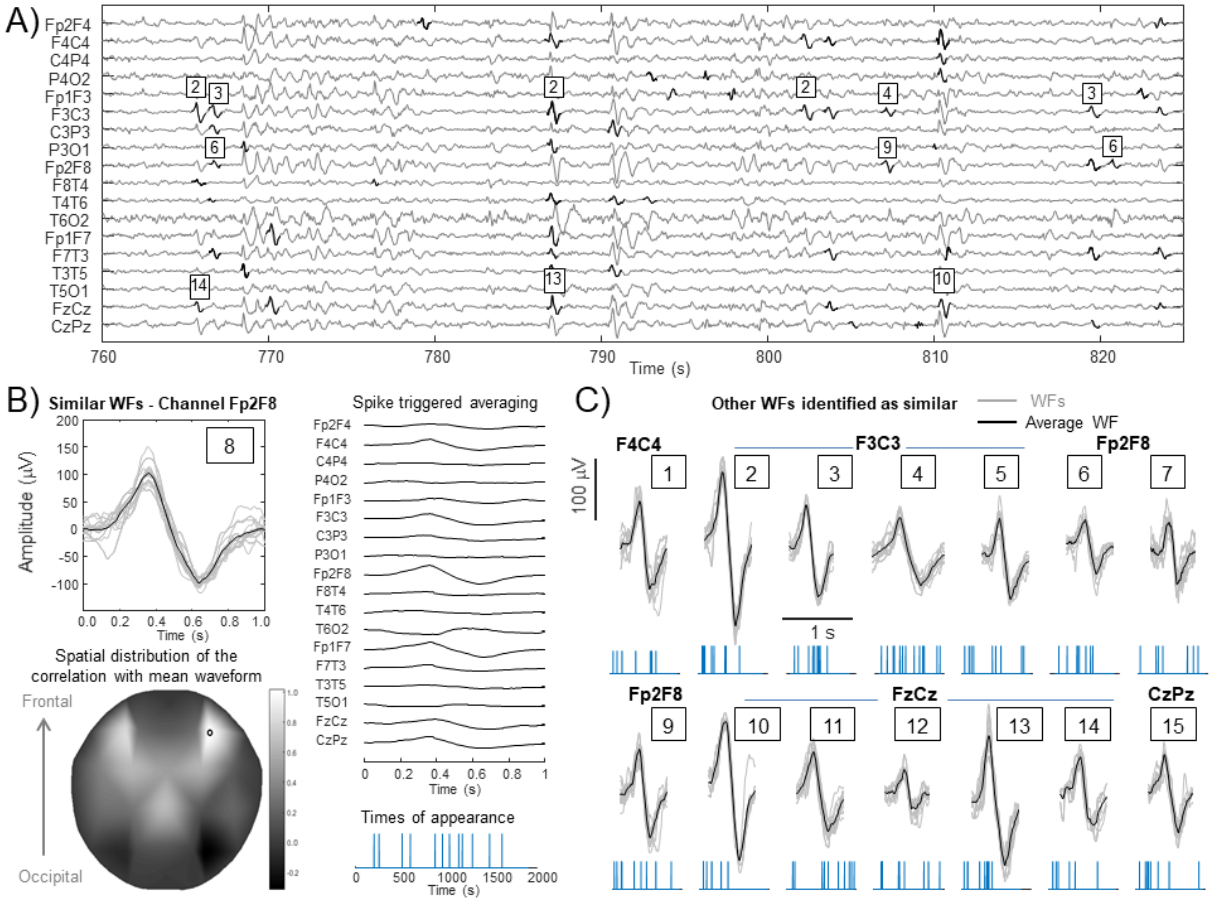

Figure 3. Example of processing of data of a patient with severe manifestations of encephalitis. A) Portion of EEG data with the waveforms (WF) identified by the algorithm shown in black. The WFs were clustered considering location, sign, amplitude and duration as features and the classes with more than 8 members were further studied. The WFs belonging to a class are indicated by the class number written over them. B) Example of a class of similar WFs (class number 8). The members and their average are shown. Moreover, the times of appearance (considering the entire experiment, lasting more than half an hour) and the averaging of EEG epochs centred on each appearance are shown. Finally, the correlation of the averaged WFs in all channels with Fp2F8 (i.e., the channel in which the SBC was found) is shown (the correlation was normalized with respect to the energy in Fp2F8). C) For all other classes than that considered in B), the WFs are shown superimposed and averaged. The spatial location and the times of appearance are also shown.

Example of advanced post-processing

Figure 3 shows an example of processing of the data from a patient with severe illness. The waveforms identified by the algorithm were clustered by a simple classification algorithm, which performed reasonably well in grouping waveforms of similar shape. Specifically, a k-

means approach was applied considering SBC location, sign, amplitude and duration as features. The number of clusters was increased until the maximal RMS within class was lower than 10% (percentage expressed with respect of the mean of the features). Then, only the classes with more than 8 members were considered.

Fifteen classes were found for the considered EEG. Notice that most of the classes group waveforms were found in the frontal channels. The repetition of the same SBC can be considered as an indication that the waveform has a clinical relevance and was not found by chance. The other SBCs, usually found in channels other than in frontal position, are mostly sporadic waves of different shapes (i.e., similar to the SBC prototype, but with different locations, amplitudes or durations). Averaging EEG epochs centred on the complexes that are members of a class (as in Figure 3B), waveforms emerge in all channels and correlate with the class average (50% of the channels show a correlation larger than 80%[1]; in the figure, the correlation is normalized with respect to the energy of the class average waveform, in order to provide information also on the different amplitude distributions).

Spatial distribution of complexes

Figure 4 shows the distributions of the number of complexes identified by the algorithm and of their RMS amplitude averaged across different EEG traces recorded either from subjects in normal conditions or from patients with serious manifestations of encephalitis. The distribution over the scalp was computed by cubic interpolation: in this way, data sampled using either 10 or 18 channels could be included. The number of complexes and the sum of their RMS amplitudes were divided by the duration of the experiment, obtaining a rate expressed in terms of either the number of identified SBCs per s or their compound amplitude per s. Wilcoxon signed rank test indicated that the number of identified complexes and their RMS amplitude were larger in the frontal channels (with significant and highly significant difference, respectively) only when the illness was serious; in the other cases, the difference was not significant (even if similar waveforms that are consistently repeated during the experiment are usually found in frontal channels also in the case of severe illness, as shown for the specific data considered in Figure 3).

[1] The correlation is here defined normalized with respect to the RMS of the two tested waveforms, so that it ranges between -1 and 1.

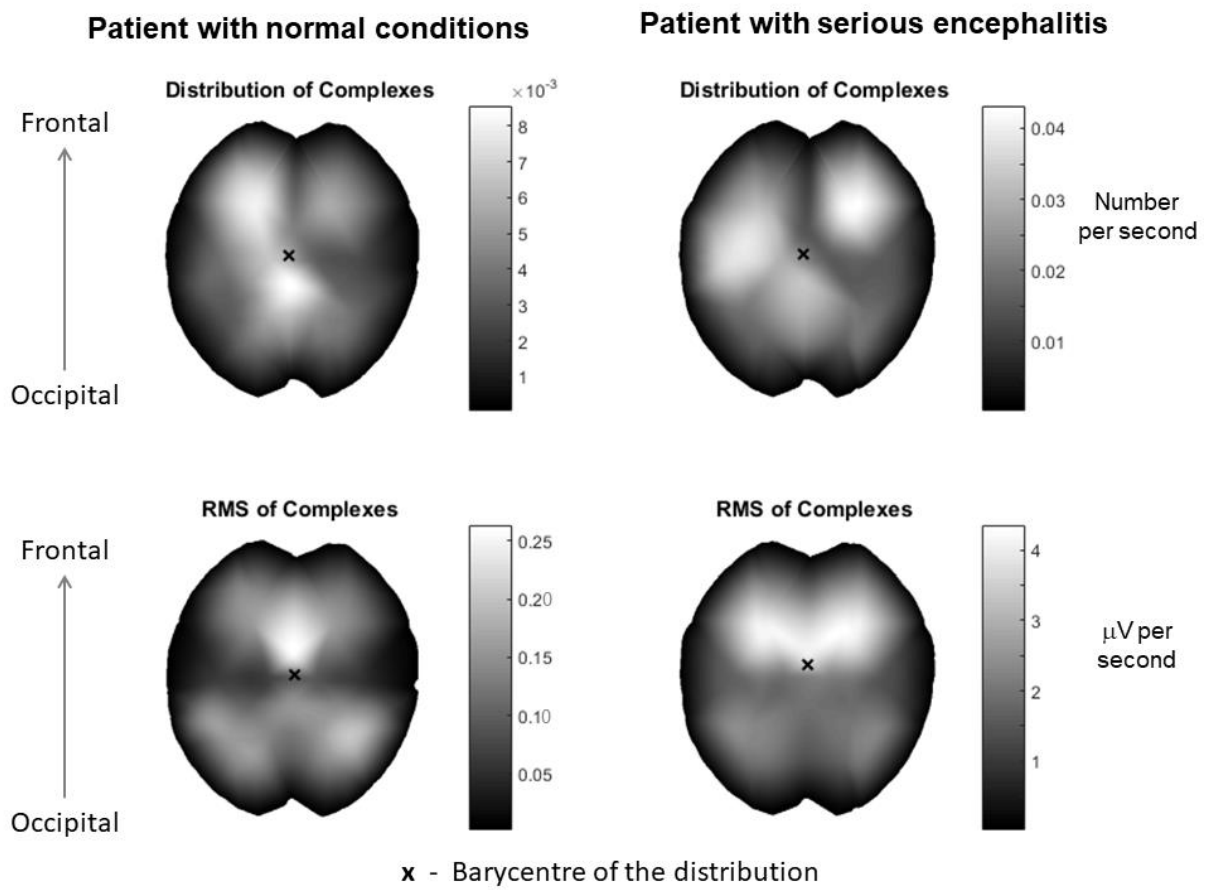

Figure 4. Distribution of complexes identified by the algorithm and of their RMS amplitude averaged across the whole EEGs recorded either in normal conditions (left, number of EEG N=22) or in case of serious manifestations of encephalitis (right, N=20).

Occurrence of SBCs in patients with different severity scores

Figure 5 shows the distribution of the number of SBCs and of the sum of their RMS amplitudes (averaged with respect to the number of channels and duration of the experiment) found either in all channels or in the frontal ones, splitting the data in different groups with same gravity score of the illness.

Kruskal-Wallis test indicates that there is a significant effect of the gravity score on all distributions. Wilcoxon rank sum test was applied on all pairs of scores (only the cases NC, i.e., those for which the gravity score was not available, were excluded). All pairs for which the scores were more different than 1 step (e.g., score 0 versus 2, or 2 versus 4) provided highly significant differences. Close conditions, for which the scores differed only by one (i.e., score 0 versus 1, 1 versus 2, etc.), showed statistically significant differences in the cases indicated in the figure. Notice that, when considering the amplitude of the identified complexes, all conditions are statistically different.

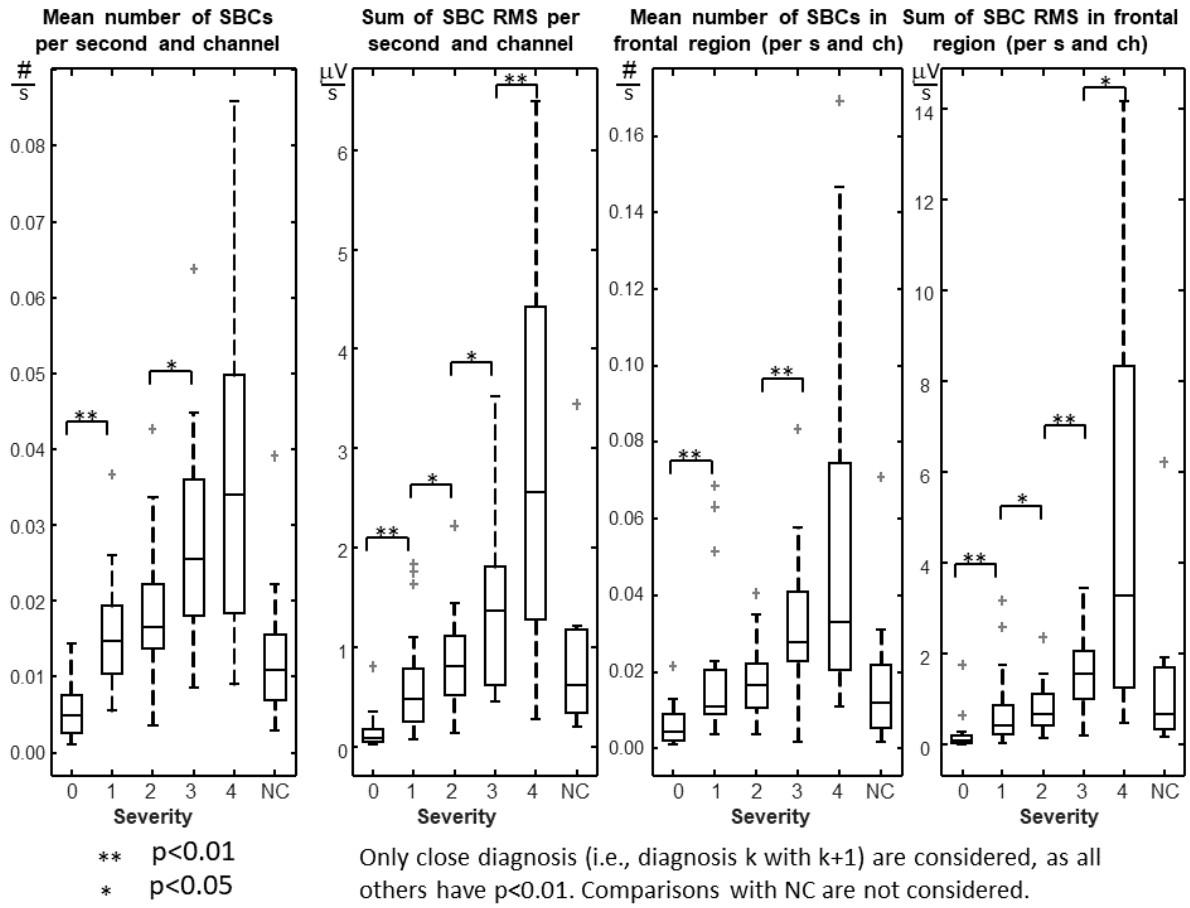

Figure 5. Distributions (median, quartiles, range and outliers shown individually) of SBCs and their amplitudes (dividing by the number of channels and by the experiment duration) identified by the algorithm either in the whole channels or in those located in frontal region from data corresponding to different severity scores. Statistical differences of pairs of close conditions (i.e., with scores differing of 1) are indicated (when scores differed of at least 2, differences were always highly significant).

Follow-up

Figure 6 shows the follow-up of patients. All indexes already considered in the previous figure are shown, grouping the data of each subject. The cross-correlation was computed between the severity score over time and either the rate of appearance of the SBC (number of identified waveforms per channel and s) or the average RMS amplitude. High correlations were found (as shown in Figure 6B), indicating a good support provided by the estimated indexes in the follow-up of the patients.

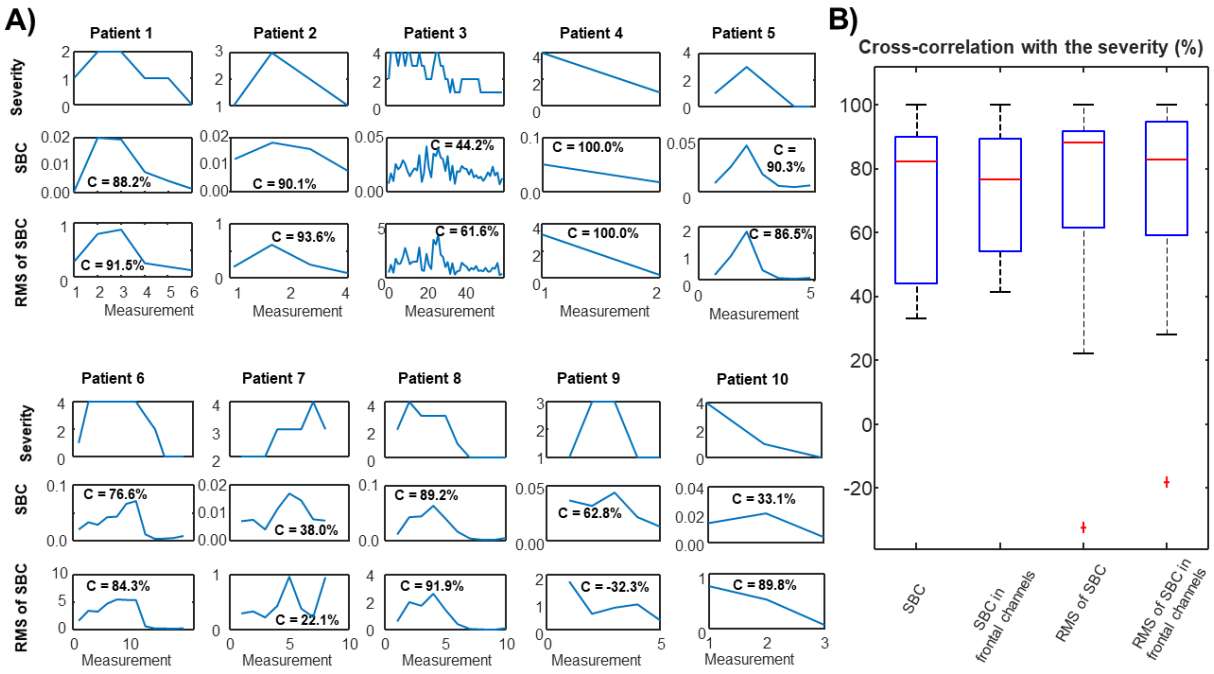

Figure 6. Investigation of the follow-up of patients. A) The number of SBCs (per channel and second) and the sum of RMS amplitudes of SBCs (μV per channel and second) are shown for each patient together with the severity score during the follow-up. The cross-correlation C between the estimated index and the severity is also indicated. B) Distributions (median, quartiles, range and outliers shown individually) of the cross-correlation between the severity score and the number of SBCs, the number of SBCs in frontal channels, the sum of RMS amplitudes of SBCs and the sum of amplitudes of SBCs in frontal channels (all indexes were divided by the number of channels and the duration of the experiment).

Discussion

Encephalitis is considered as a serious problem and subjects frequently report neurological sequelae. Fast assessment of CNS inflammation is fundamental to reduce morbidity and mortality [2][3][9]. The diagnosis of encephalitis is based on the integration of several clinical data. Patients show primarily encephalopathy or an altered level of consciousness (lethargy, irritability or personality variations). Moreover, different evaluations are made to check if two or more of the following problems are present: fever, seizure, focal neurologic deficit, neuroimaging abnormality (i.e., lesions on either MRI or CT), pleiocytosis of CSF (extracted by a lumbar puncture). EEG traces are also investigated to assess if there are abnormalities, subjectively identified by expert neurologists. EEG investigation is economic and non-invasive and can provide detailed information on the state of the brain. Several studies in the literature showed that EEG features are strongly influenced by the aetiology of the diseases (like vascular

or metabolic diseases) [10]. From this perspective, EEG allows to advance diagnostic hypotheses and to outline possible factors outcome related [11]. Early EEG disorders are often associated with negative prognostic factors and support aggressive neuroprotective anti-inflammatory therapeutic strategies [11]. The automated processing of EEG removes the subjective interpretation of the traces and, in some studies, it was found to be more reliable and repeatable than visual assessment [10][20][21][22][23].

In this paper, we investigate EEGs from patients with encephalitis. This inflammatory disease, if not timely treated, may lead to permanent damages and a great burden for society [3][13][24]. SBCs were visually identified and reported in some works [14][15][16][17][18][25][26][27]. Few reports described EEG changes in Rasmussen's syndrome, which is a rare pathology with focal onset [28][29]. In these cases, slow lateralized EEG activity was reported as an early finding [30]. Focal delta activity without inter-ictal epileptiform abnormalities was also found [31] in contrast to the early appearance of SBCs [16][32].

Some automated EEG processing approaches were developed to support the interpretation and diagnosis of encephalitis: systematic fluctuations of the excitatory and inhibitory connectivity gains were found by fitting seizures of anti NMDA-R encephalitis with dynamic causal models [33]; a reduced complexity of EEG was found in patients with respect to controls [34]. However, no automated method has been proposed in the literature to identify SBCs.

The slow activity, either focal (as in the case of Rasmussen's syndrome mentioned above) or diffused (as in the majority of the inflammatory processes), can interfere with the visual identification of SBCs. Thus, an automated method for SBC identification is needed. This could help to overcome the subjectivity of a manual identification, which is operator dependent. Moreover, once identified the complexes, quantitative and objective information can be retrieved, e.g., by computing the average rate of appearance of all SBCs or of the complexes generated by different sources. An automated method can also be efficient, as long traces could be processed in few minutes and even small amplitude complexes can be identified.

Here we propose the first tool for the detection of SBCs. It is based on a set of match filters. Specifically, the raw EEG was cross-correlated with scaled versions of a prototype waveform identified after decades of observations of SBCs in different pathologic traces. The use of rescaled templates allowed to identify efficiently the SBCs, as they emerge from background activity with a shape which could also be scaled in time. Our method is related to match filtering [35][36] and to the many works with the aim of finding a specific waveform within a signal [37][38]. However, different SBCs can have varying scaling, so that multiple filters were required. This approach is similar to that of continuous wavelet decomposition (that also found

many applications in EEG studies [39]) even if a normalized correlation was here considered. Thus, the algorithm had some properties required by the specific application, so that it was implemented without adapting to other available techniques.

Once identified the SBCs, different quantitative analyses can be considered: topographical distribution, rate of appearance, classification of the different waveforms and analysis of their frequency or distribution on different channels (e.g., to extract the location of the source) [40]. Some representative examples of processing are displayed in Figures 1-4. Figure 1 shows the prototype waveform and the identification of SBCs in some EEGs from patients in different conditions. Figure 2 shows the rate of appearance of SBCs, comparing a normal EEG trace (in which sporadic identifications of SBCs are due to chance) and that of a patient. The latter showed more SBCs and structured statistics of their times of appearance and distribution of SBC amplitudes. Moreover, spatial distribution was not random, as in the case of the few SBCs found on the EEG of the healthy subject: most SBCs were found in frontal channels on the patient. Figure 3 shows how SBCs can be divided into clusters with similar morphology. Ideally, these clusters indicate the repeated activity of the same sources, whose frequency and spatial distribution can be investigated. Most clusters found in the representative EEG considered (from a patient) were located on frontal channels. SBCs found in other channels did not fire regularly, so that they could result from sporadic activity or random occurrence of a waveform similar to a SBC. Figure 4 considers the average topographical distribution of the SBCs found in different subjects grouping the cases with the same severity scores. Normal controls and patients with serious manifestations of encephalitis are shown: the distribution is random for controls, whereas it shows a peak on frontal channels for the patients, confirming the results of the previous figures, suggesting a predominant manifestation of SBCs on frontal channels (in line with other studies [15]).

The entire dataset is considered in Figures 5 and 6. Figure 5 shows that the number and the average amplitude of complexes increase with the severity score. Statistical differences were found at least for an index, comparing all possible group pairs. All data were put together, without considering that some measurements were repeated on the same subjects. Data of different subjects were instead separated in Figure 6. The number of identified SBCs and their average amplitudes were compared to the severity score by cross-correlation. The median correlations were around 80%, indicating that the indexes can be useful in the follow-up of patients. Figures 5 and 6 show that focusing only on frontal channels does not improve significantly the discrimination capabilities of the two indexes. However, the preliminary indications of the previous figures suggest that the spatial distribution of the sources of SBCs

is not random, but predominant in the frontal region. A statistically larger average number and amplitude of SBCs was found in frontal channels only for the largest severity score. However, the dataset included only few subjects, so that it should be extended to confirm our preliminary results and make them statistically more robust.

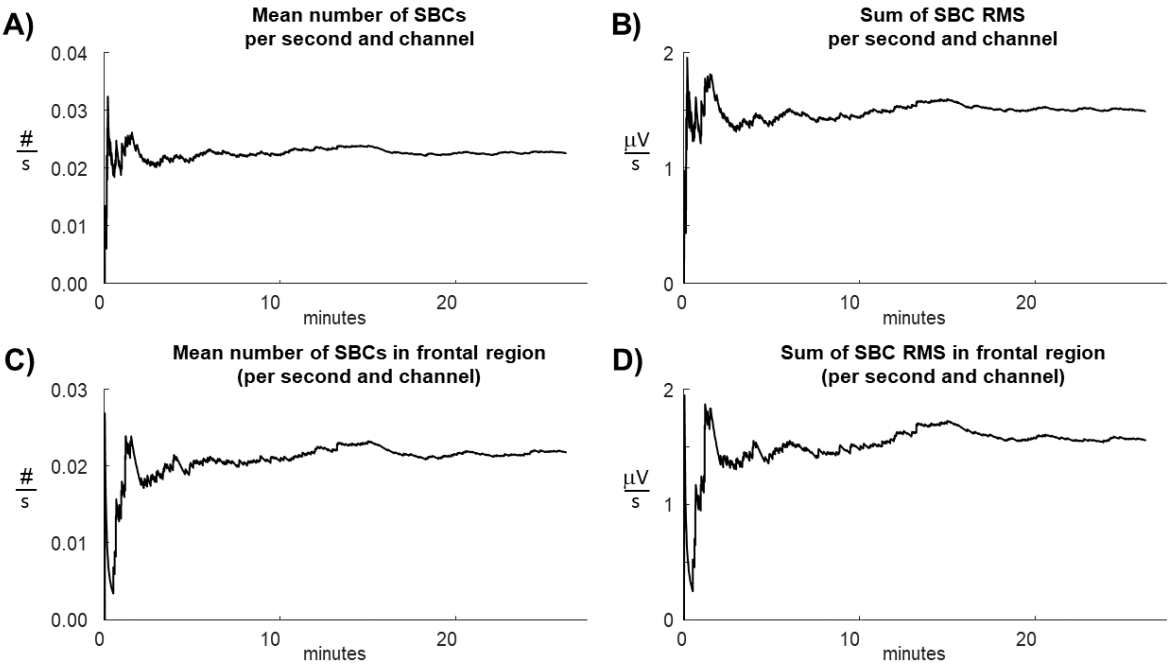

Figure 7. Estimation of A)-C) mean number of SBCs, B)-D) their cumulative RMS amplitude (divided by the number of channels and the duration of the trace in seconds), computed either A)-B) in all channels or C)-D) in the frontal ones, as a function of the duration of the EEG trace (representative subject with severity score equal to 4).

The appearance of SBCs was found to be about stationary in the investigated EEG traces. Indeed, similar results could be obtained by processing only the first few minutes instead of the entire traces (mean duration of our traces was about 17 minutes and 20 s). For example, the rate of appearance of SBCs and their cumulative RMS amplitude stabilize after 5-10 minutes (depending on the trace and on possible non stationarity, like as the progressive entering of the subject in a drowsiness condition). Figure 7 shows an example of estimations obtained as a function of the duration of the trace, in the case of a serious patient. After the first minutes, the estimations stabilize, showing that the appearance of the SBCs is about stationary. Not shown results indicate that, even using only the first 4 minutes of our traces, all severity scores could be statistically distinguished by at least one of the indexes shown in Figure 5, with the exception of scores 1 and 2 (when the appearance of SBCs is rare, longer traces are needed to assess them accurately; however, healthy subjects, showing only sporadic appearance of waveforms similar

to SBCs, were distinguished from all patients, even the mild ones, by all 4 indexes with highly significant statistical confidence). Also the spatial distributions of SBCs and of their cumulative amplitude are stable when estimated from few minutes of EEG traces: Figure 8 shows how the correlation with the spatial distribution estimated from the entire EEG increases when considering longer traces (however, notice that the median correlation is higher than 80% even considering short traces of only 4 minutes).

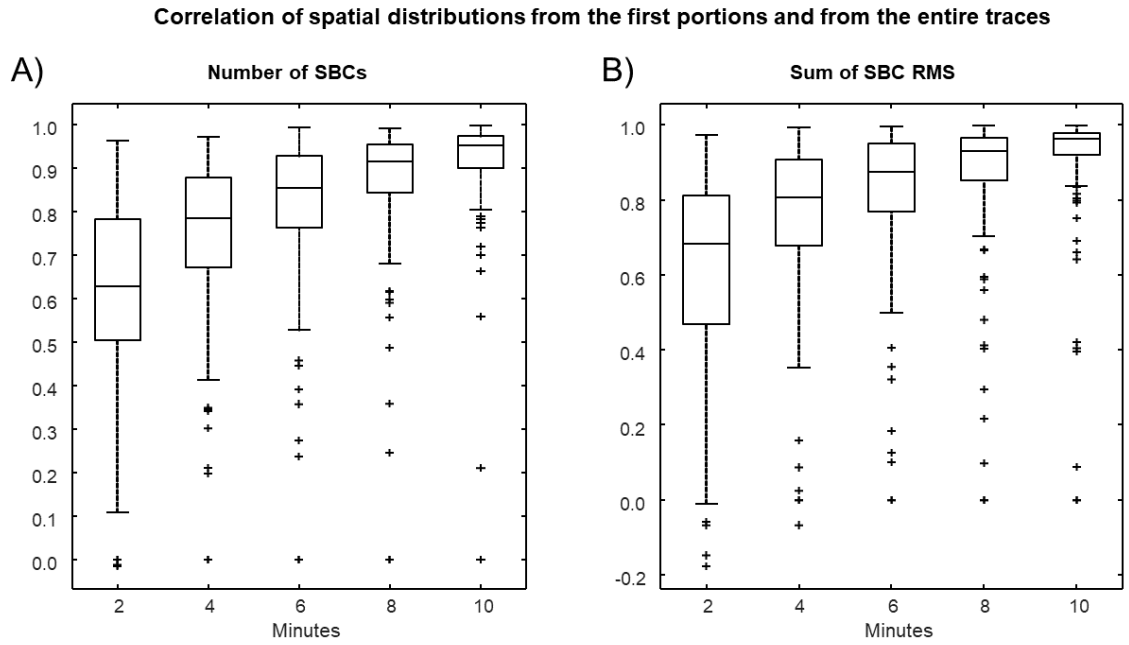

Figure 8. Correlation (given in terms of median, quartiles and range, with outliers shown individually) between the spatial distribution of either A) the number of SBC or B) their cumulative amplitude, estimated considering either the initial portions (in the range 2-10 minutes) or the entire EEG traces (different durations with mean about 17 minutes).

In summary, our results show a clear correlation between the appearance of SBCs in EEG and the severity of encephalitis. The number and amplitude of identified SBCs allow both to compare different patients and to monitor a single patient over time. A recent work showed that better accuracy in identifying the severity scores could be obtained by optimally integrating the information contained in SBC indexes by a binary classification tree [41].

Even short EEG traces (of about 5-10 minutes) can be enough. Hence, our algorithm could be useful to speed up the diagnosis procedure and to identify more accurately the therapeutic intervention to be performed, thus decreasing both the complications associated with the morbidity event and mortality. Moreover, it allows to deepen the mechanisms underlying the formation of the SBCs, by separating and investigating different sources. Being rapid, economic

and non-invasive, our technique could also support the follow-up of patients. Further validation and analysis studies are in progress to support these important outcomes.

Conclusions

The CNS inflammatory pathology can have very serious sequelae and the quickness of the diagnosis and targeted therapeutic interventions are important. EEG is a fundamental tool as an indicator of inflammatory cause and for monitoring the clinical situation. A new automated system for the analysis of EEG paths is here proposed to identify SBCs. Our results indicate that the onset of SBCs correlates with clinical data.

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