Automated diagnosis of encephalitis in pediatric patients using EEG rhythms and slow biphasic complexes

Physical and Engineering Sciences in Medicine manuscript No.
(will be inserted by the editor)

Automated diagnosis of encephalitis in pediatric patients using EEG rhythms and slow biphasic complexes

Luca Mesin · Massimo Valerio · Giorgio Capizzi

Received: date / Accepted: date

Abstract Slow biphasic complexes (SBC) have been identified in the EEG of patients suffering for inflammatory brain diseases. Their amplitude, location and frequency of appearance were found to correlate with the severity of encephalitis. Other characteristics of SBCs and of EEG traces of patients could reflect the grade of pathology. Here, EEG rhythms are investigated together with SBCs for a better characterization of encephalitis.
EEGs have been acquired from pediatric patients: 10 controls and 10 encephalitic patients. They were split by neurologists into five classes of different severity of the pathology. The relative power of EEG rhythms was found to change significantly in EEGs labeled with different severity scores. Moreover, a significant variation was found in the last seconds before the appearance of an SBC. This information and quantitative indexes characterizing the SBCs were used to build a binary classification decision tree able to identify the classes of severity. True classification rate of the best model was 76.1% (73.5% with leave-one-out test). Moreover, the classification errors were among classes with similar severity scores (precision higher than 80% was achieved considering 3 instead of 5 classes). Our classification method may be a promising supporting

L. Mesin
Mathematical Biology and Physiology, Department of Electronics and Telecommunications, Politecnico di Torino, Corso Duca degli Abruzzi 24, Torino, 10129 ITALY
Tel.: +39-0110904085
Fax: +39-0110904099
E-mail: luca.mesin@polito.it

M. Valerio
Mathematical Biology and Physiology, Department of Electronics and Telecommunications, Politecnico di Torino, Turin, Italy
E-mail: massimo.valerio@polito.it

G. Capizzi
Ospedale Infantile Regina Margherita, Department of Child Neuropsychiatry, Universitá di Torino, Turin, Italy
E-mail: giorgio.capizzi@unito.it

tool for clinicians to diagnose, assess and make the follow-up of patients with encephalitis.

Keywords EEG · EEG rhythms · Encephalitis · Slow Biphasic Complex · Binary Classification Decision Tree.

1 Introduction

Encephalitis reflects a brain inflammation associated with neurological problems [21][40][52][57]. In children, its incidence is about 1 out of 10,000 [59]. The lethal rate is high: for example, encephalitis by herpes simplex (i.e., the most common etiologic agent) has a mortality rate in the order of 5-20% (which rises to 70% if an antiviral treatment is not applied [12]). Encephalitis can be caused by infectious diseases, immune disorders, vascular pathology or cancer [5]. The rapid diagnosis of the pathology is of primary importance to reduce deleterious consequences [5][31][40]. However, its assessment is mostly subjective, based on the integration of many clinical observations (e.g., about body temperature and level of consciousness) and measurements (e.g., imaging, blood tests, analysis of the cerebrospinal fluid).

The EEG was found to be useful for the assessment of different kinds of encephalopathy [20][48][51][55]. A wide variability of EEG activity is present in childhood especially during the rapid brain development that occurs in the newborns [29][44]. However, the EEG has characteristics similar to adults already at the end of the first year of life [29]. The sleep elements occur around the third month reaching their maturity at around two years [44].

The EEG has also been investigated in the case of patients with suspected encephalitis [49], by neurologists looking for possible anomalies. Its use is fairly appreciated as the recordings are fast, non-invasive and economic, thus allowing to be applied in emergency and in the follow-up. However, EEG traces are usually assessed subjectively by experts and only qualitative information (e.g., about the presence of anomalous waveforms) is usually extracted. The automated EEG processing for its interpretation would remove the subjective analysis of the traces and provide quantitative information which could be very useful for a detailed assessment of the condition of the patient and identification of the proper therapy.

A waveform which has been found to emerge in patients with brain inflammations is the slow biphasic complex (SBC) [7][8][9][13][15][23][26][32][50]. After being observed during decades in EEG traces of patients with different pathologies (e.g., human immunodeficiency virus - HIV [7][8], West syndrome [15][50], encephalitis [7] and Rasmussen's syndrome [9]), we proposed an automated method to identify it [37]. We found a high correlation of the number and amplitude of the identified SBCs with the severity of encephalitis. This information was further used to identify automatically a severity score associated to each EEG trace by the medical doctors, considering both electrophysiological and clinical data. Specifically, a binary classification decision tree was

developed, based on quantitative indexes characterizing SBCs [38]. The performances (predictive value of about 60%) were good enough to further indicate that SBCs indeed contain important information on encephalitis, but not so high to provide a reliable clinical diagnosis. Thus, other investigation, e.g., on body temperature, level of consciousness, focal neurologic deficits and possible seizures, was suggested to be still considered to refine the clinical picture [38].

In order to provide a more reliable identification of the severity of encephalitis using only electrophysiological data, here we extend our previous method by including also information on EEG rhythms. Their relative power was found to be specific of different tasks [60], levels of consciousness [42] and pathologies [36]. Since its onset, encephalitis mainly shows slow focal or diffused electrical activity often associated with other various anomalies, including epileptiform anomalies (e.g., periodic discharges) [4][41][48][49]. Moreover, EEG rhythms have been recently used for the diagnosis of encephalopathy [27], showing a larger relative contribution of slow waves (with significant increase of delta and decrease of alpha and beta rhythms). Thus, it is reasonable that they could provide useful information also on the severity of encephalitis. In this paper, we investigate both their average relative power in the EEG traces and how they change before the onset of an SBC. This information on EEG rhythms, together with properties of the identified SBCs, was included in the set of input features of a classifier aimed at identifying the severity of the encephalitis.

2 Methods

2.1 Automated detection of SBCs

SBCs were identified by the algorithm proposed in [37]. Specifically, SBCs have been manually identified in decades of clinical observations. They were then averaged, obtaining a waveform that was considered as a prototype of complex to be identified in new EEG traces (see Figure 1A). SBCs were then found automatically by the use of match filtering [11][45], applied on EEG data band-pass filtered between 0.1 and 30 Hz. Specifically, the EEG traces were compared to 10 time-scaled versions of this prototype waveform [37]. A template matching was identified when the cross-correlation was at least 90%. The method was adapted to the qualitative information acquired by clinical experience. In particular, repetitive appearance of SBCs was excluded; moreover, the complexes should emerge from background EEG. Finally, they may have different amplitude and duration, but with a positive correlation between them, so that different complexes appear to be approximately time-scalings of the same waveform, with similar magnification along the amplitude and time directions. These indications were used to review automatically the candidate waveforms identified by the match filters. Specifically, identified waveforms showing repetitive discharges or with amplitudes which were either very large or low (probably related to artifacts or noisy oscillations, respectively) were removed.

Examples of automatically identified SBCs are shown in Figure 1, in the cases of a control subject and two patients with either moderate or serious manifestations of encephalitis. Notice that in the healthy subject only few waveforms are identified: they have a slow biphasic shape that resembles a complex, but these identifications are false positives. On the other hand, many complexes are identified in the EEG traces of the patients (with appearance rate and cumulative amplitude of SBCs directly related to the level of severity of encephalitis).

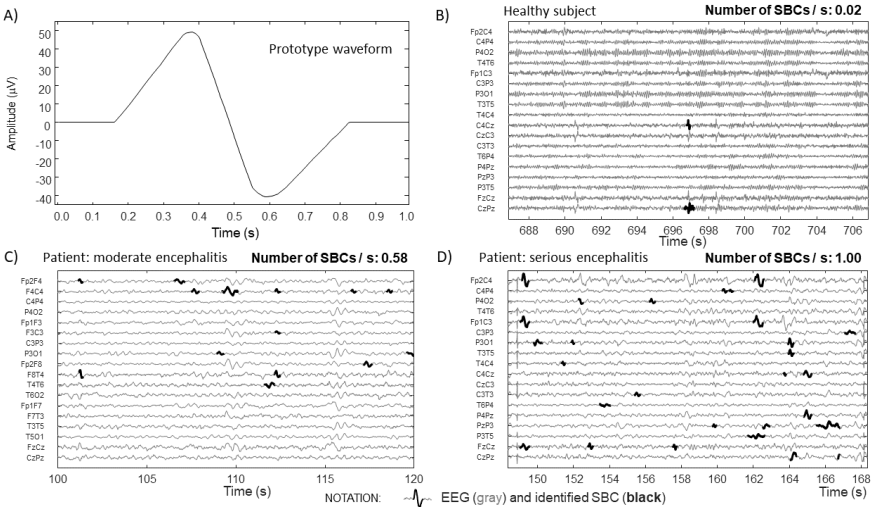

Fig. 1 Slow biphasic complexes (SBC) and examples of processing of portions of EEG recordings. A) Waveform used as prototype to identify SBCs. B) Waveforms similar to an SBC automatically identified in an EEG trace recorded from a control subject (root mean square amplitude is about 9 μV). C) SBCs automatically identified in an EEG trace from a patient with moderate encephalitis (root mean square amplitude of about 40 μV). D) Processing of an EEG from a patient with serious encephalitis (root mean square amplitude of about 7 μV).

2.2 Relation between SBCs and EEG rhythms

Not published personal observations of the authors indicate that SBCs are more common during hyperventilation than in rest conditions and in waking than during sleeping. EEG rhythms are affected by many conditions, including the level of consciousness, the mental task and pathologies. Thus, it was reasonable that the relative power of different EEG rhythms could change depending on the severity of the encephalitis. Moreover, we suspected that the EEG rhythms could change before the appearance of an SBC.

Then, the delta (1-4 Hz), theta (4-8 Hz), alpha (8-13) and beta (13-30 Hz) rhythms were estimated. Band-pass Chebyshev type I filters of order 6 were

used to select the bandwidths of interest. They were run in both directions to remove phase shifts and distortion. In this way, time series including the specific frequency ranges were obtained. Their instant powers were computed as the squared of each time sample, further smoothed by a low-pass filter with cut-off equal to the lower frequency bound of the rhythm divided by 4 (again, anti-causal zero-phase Chebyshev type I filters of order 6 were used). Then, their relative contributions were obtained by the ratio between the power of the rhythm of interest and the sum of the powers of all 4 rhythms. In this way, the relative power of each rhythm was obtained as a function of time. These time series were averaged over different intervals of interest: the mean of all samples provided the average contribution of the rhythm in the entire EEG trace; the mean of all samples in intervals of 2 s duration preceding each SBC was also considered as an indicator of the average contribution before the onset of a complex.

Examples of SBCs are shown in Figure 2 together with the contributions of the different EEG rhythms.

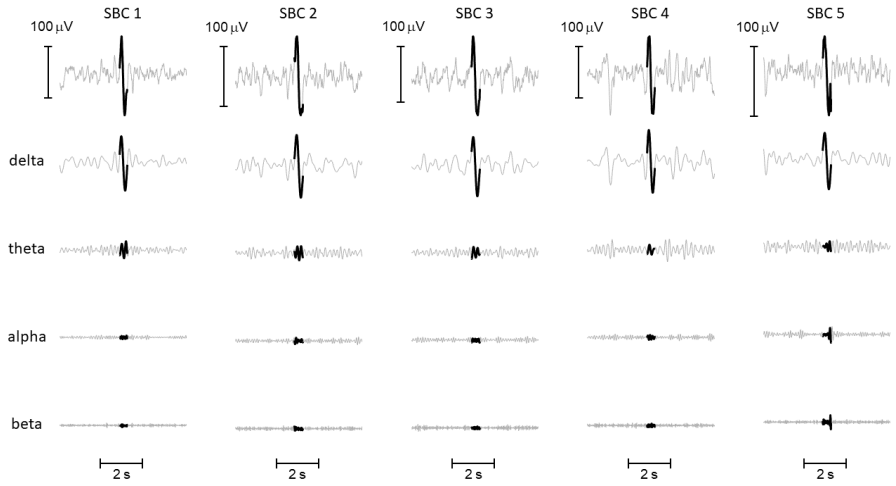

Fig. 2 Examples of SBCs extracted from a patient (the same as in Figure 1D; the 5 largest SBCs are considered). The raw signal portions are shown above; below them, the contributions in the delta, theta, alpha and beta ranges are provided.

2.3 Experimental data

We considered the same dataset as in [37] and [38]. A Micromed system (sampling frequency 256 Hz, analog band-pass filter with bandwidth 0.5-70 Hz) was used with different set-ups, including either 10 or 18 bipolar channels, to acquire 128 spontaneous EEGs from pediatric subjects: 10 patients with

encephalitis (age 2-14 years; 5 males and 5 females) and 10 controls (age 1-15 years; 5 males and 5 females).

Control subjects were monitored only once, whereas patients were followed-up for a period ranging from few weeks to months. Different levels of severity of the pathology were observed in the follow-up of patients. It was assessed on the basis of the following data: possible seizures and focal neurological deficits, body temperature, level of consciousness, lesions on either computerized tomography or magnetic resonance, cerebrospinal fluid pleiocytosis. Finally, EEG traces were observed by expert neurophysiologists, looking for possible abnormalities, e.g., some SBCs identified subjectively. This subjective electrophysiological evaluation was integrated to the available clinical information (recorded in the same day of the EEGs) to associate to each trace the severity of the pathological condition, indicated by the following scores:

0 normal condition (shown by either patients, in a period in which they manifested no sign of disease, or controls; assigned to 22 traces);
1 mild disease (assigned to 29 traces);
2 moderate disease (assigned to 25 traces);
3 severe condition (assigned to 22 traces);
4 serious pathology (assigned to 20 traces);
NC not classified (assigned to 10 traces which were not manageable).

Not manageable signals were excluded, thus considering a database of 118 EEGs.

2.4 Algorithm to identify the severity scores

A multi-class estimation problem was faced to identify the severity score (5 classes, from 0 to 4) associated to the EEG traces. It is a classification problem aimed at identifying the correct severity using features extracted from our EEG data. The problem requires to select both optimal input features and a reliable classifier. Three different classification approaches were tested in the same conditions: the error-correcting output codes (ECOC) model, using support vector machines (SVM) for binary one-to-one classifications [22][30]; the Naive Bayes classifier (estimating data distributions using smoothed densities with normal kernel); the binary tree model (BTM) [53]. As the BTM provided best results (in terms of a 10-fold cross-validation test), in the following we'll focus only on it.

A BTM splits sequentially the data in two groups, on the basis of a test on a specific feature. The features to be used, how many divisions to consider and the threshold for each test should be chosen.
We considered the following set of features, including information about the number, amplitude and spatial distribution of SBCs (selected by the best classifier in [38]) and the additional properties related to EEG rhythms:

1. number of SBCs automatically identified (divided by the duration of the EEG and the number of channels);

2. cumulative root mean square (RMS) of SBCs (i.e., the sum of the RMSs of SBCs divided by the duration of the trace and the number of channels);
3. number of SBCs in the frontal channels (again normalized by EEG duration and channel number);
4. cumulative RMS of SBCs in frontal channels (with same normalization as before);
5. relative average power of delta rhythm in the 2 s before the SBCs;
6. relative average power of theta rhythm in the 2 s before the SBCs;
7. relative average power of alpha rhythm in the 2 s before the SBCs;
8. relative average power of beta rhythm in the 2 s before the SBCs;
9. relative mean power of delta rhythm in the entire EEG trace;
10. relative mean power of theta rhythm in the entire EEG trace;
11. relative mean power of alpha rhythm in the entire EEG trace;
12. relative mean power of beta rhythm in the entire EEG trace.

Notice that the relative average powers of the rhythms in the entire EEG and in windows of 2 s before the SBCs were both kept as they were found to be statistically different (paired Wilkoxon signed rank test, $p << 0.01$). Specifically, the relative contribution of the delta rhythm was statistically greater before the SBCs than in the entire EEG, whereas all other rhythms were smaller. Thus, the EEG was found to slower (as low frequency contributions increased) before the onset of an SBC.

An exhaustive search was implemented, considering all possible combinations of features as inputs of different BTMs. The implementation of the BTMs was based on functions available in MATLAB R2019a (The Mathworks, Natick, Massachusetts, USA). Gini's diversity index was used as splitting criterion. All possible combinations of choices was considered and the best categorical predictor split was then chosen on the basis of a cross-validation test with 10 folds. As the model could be still complicated (i.e., it could include many features and data divisions), it was pruned selecting the smallest tree with a number of misclassified observations within one standard error of the minimum. This model was then proposed for the identification of the severity scores. Its performance was tested by a leave-one-out approach (i.e., each single sample was used for test of the BTM trained on the rest of the data; this method was chosen due to the small size of our dataset).

3 Results

Figure 3 shows the distributions of the features selected by the best BTM (i.e., the one with best generalization and after pruning). They are the number of SBCs identified in the frontal lobe (also selected by the best BTM in [38]) and two features related to EEG rhythms: the relative average power of alpha and theta rhythms in the 2 s before the onset of SBCs. All features were statistically affected by the severity scores (Kruskal-Wallis test, $p << 0.01$). Notice that there is at least one index for which the difference between close

severity scores can be statistically discriminated (Wilcoxon rank sum test, $p < 0.01$).

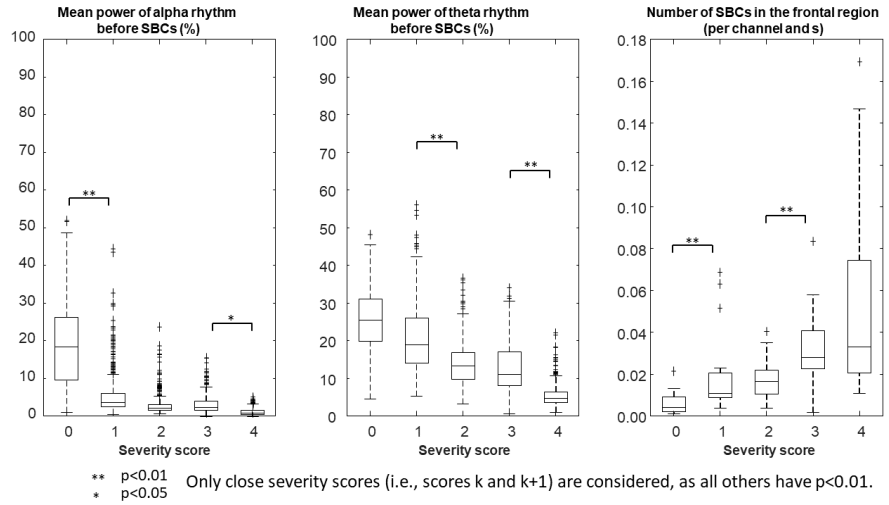

Fig. 3 Distribution of the features selected by the best classifier (statistically significant differences assessed by the Wilcoxon rank sum test; the average power of the rhythms are considered for all identified SBCs, which were more than 2 thousands, whereas the total number of SBCs in the frontal channels was computed for all manageable EEG traces, i.e., 118).

Figure 4 shows the best BTM selected after training on the entire dataset, 10-fold cross-validation and final pruning. Notice that the powers of theta and alpha rhythms before SBC onset (features x_6 and x_7 in Figure 4) decrease for larger severity scores (as shown in Figure 3); on the other hand, the number of identified SBCs increases with the worsening of encephalitis (feature x_3, i.e., the number of SBCs in frontal location). In fact, the first tests (starting from the top of the BTM) select the extreme conditions (i.e., severity scores equal to either 0 or 4) on the basis of the powers of the rhythms (x_6 lower than a threshold for score 4, x_7 larger than another for score 0); then, the number of SBCs is considered to discriminate score 3 from lower values (a number of SBC larger than a threshold is imposed to identify score 3); finally, score 1 and 2 are discriminated imposing a larger power of theta rhythm for the first. The confusion matrix of this BTM is given in Table 1. The severity score was correctly estimated in the 76.1% of cases; misclassification by 1 severity score was found in the 17.1% of tests; mistakes of 2 scores occurred in the 6% of cases; 1 mistake was made with 3 grades of difference; no misclassification of healthy with serious patients was obtained.

The method was also tested using a leave-one-out approach (keeping the best features selected before, but considering different training sets, as the test sample is excluded, thus getting slightly different trees). The confusion matrix

in Table 2 was obtained. Notice that there is only a small degradation of the performance with respect to the best BTM obtained by training on the entire dataset (the precision dropped from 76.1% to 73.5%, with 3 additional mistakes). This is an important difference with respect to the model obtained in [38], where the performances dropped from 64.1% (on the training set) to 55.6% (with the leave-one-out test).
As in [38], we made further tests to assess classifier performances when splitting data only into 3 instead of 5 severity scores (grouping mild/moderate in a class and severe/serious in another).
The classification was obtained by simply grouping the classes identified by the previous algorithm. Specifically, the cases estimated as healthy were included in class number 1, those with estimated severity scores equal to either 1 or 2 were placed in class 2, and those estimated as either severe or serious in class 3. The classification precision was 82.9% for the best model (trained on the whole dataset) and 82.1% when tested with the leave-one-out approach.

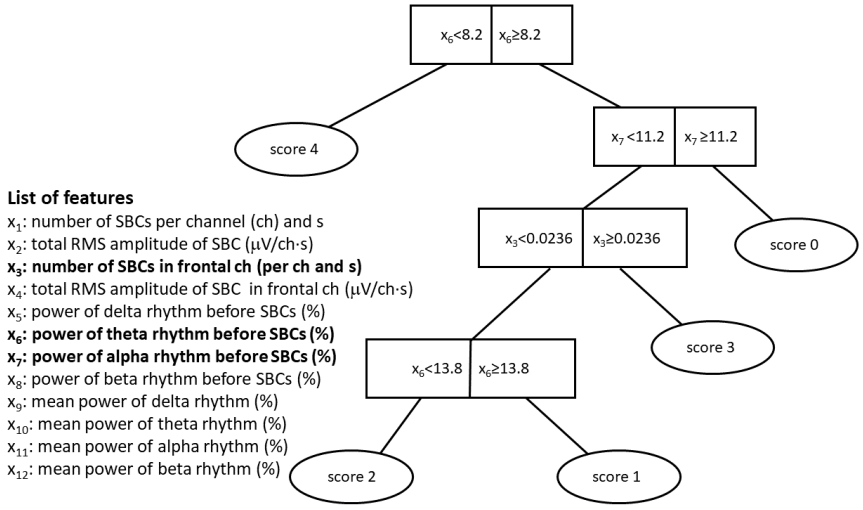

Fig. 4 Best binary tree model (BTM), selected as the one which could fit our data with best performances. The tested features are listed on the left, indicating in bold those included in the model. When a new case is considered, the active features undergo sequential binary tests (displayed as rectangles in the shown BTM), starting from the top and going on with other tests until ending on an estimated severity score.

4 Discussion

Encephalitis can have serious consequences. Frequently, it shows neurological sequelae and is an important economic burden, due to expensive monitoring and treatments in a hospital [58]. In order to reduce mortality and morbidity, the diagnosis should be reliable and fast [5][31][40]. Moreover, a non-invasive,

Table 1 Confusion matrix of the binary tree model shown in Figure 4, obtained after a training on the entire dataset (mean sensitivity 76.1%; mean specificity 93.5%; negative predictive value 93.7%; mean accuracy 89.9%).

Predicted score	**Target score**					**Predictive value**
	0	**1**	**2**	**3**	**4**	
0	19	3	1	0	0	82.6%
1	3	22	6	2	1	64.7%
2	0	1	14	3	1	73.7%
3	0	2	3	16	0	76.2%
4	0	0	1	1	18	90%
True rate	86.4%	78.6%	56.0%	72.7%	90.0%	**76.1%**

Table 2 Confusion matrix obtained by testing the best binary tree model with a leave-one-out approach (mean sensitivity 73.5%; mean specificity 93.0%; negative predictive value 93.1%; mean accuracy 89.0%).

Predicted score	**Target score**					**Predictive value**
	0	**1**	**2**	**3**	**4**	
0	19	3	2	0	0	79.2%
1	3	21	5	2	1	65.6%
2	0	2	14	2	2	70.0%
3	0	2	3	15	0	75.0%
4	0	0	1	3	17	81%
True rate	86.4%	75.0%	56.0%	68.2%	85.0%	**73.5%**

simple and economic method is needed to assess the progress of the pathology in patients and to monitor their response to therapy. However, the available diagnostic methods are based on multiple serological and instrumental examinations, for the assessment of the basic vital functions and the identification of symptoms. The most specific clinical investigations are either invasive or expensive. Moreover, emergency therapy is mostly empirical and leads to the administration of antiviral drugs, antibiotics and steroids.

EEG analysis is non-invasive and low cost, so that it is desirable to use it to obtain an objective method to diagnose encephalitis [16][19]. The SBC was found in the EEG of patients with different inflammatory diseases of the brain and was proposed as a selective marker useful for their diagnosis [6][7][8][9]. The automated analysis of EEG is finding more and more applications and is important to remove subjectivity [1][2][3][28][39][43][46][47]. An automated method was proposed for SBC identification [37]. This approach allows to overcome the problems of subjective interpretations of the traces. This is also important if we consider that only a few experts have worked in the past in this field and have the skills required to correctly identify the SBCs. Moreover, a post-processing can provide quantitative information on SBCs. For example, their number and cumulative amplitude correlate with the severity of encephalitis [37]. Furthermore, different groups of similar SBCs were found to appear in the EEG [37], suggesting that different inflamed sites (spread in the brain) were repeatedly activated.

Some features characterizing the SBCs automatically identified (e.g., rate of appearance and its variability, location and cumulative amplitude) were employed to develop a classifier to discriminate EEG traces associated to different severity of encephalitis in [38]. A simple BTM was used to face the multi-class problem; here additional approaches were tested (ECOC model with SVMs for binary one-to-one classifications and Naive Bayes model), but the BTM has still provided the best performances. Many other classification approaches have been studied in EEG processing, e.g., for brain computer interface applications [34][35] or for the identification of the phases of absence seizure [30]. A few simple and fast approaches were here considered, in order to get reliable indication of the best features for the classification of encephalitis, after making an exhaustive search (notice that making more tests with other methods should be avoided, as, with a high number of tested configurations, there is the risk of obtaining overoptimistic results due to overfitting of our small dataset [54]). The BTM allows a simple description, interpretation and implementation of our results. Specifically, different properties of the SBCs were considered as potentially useful to identify the severity of encephalitis. The features that allowed to get the best classification performances in [38] were related to the number of SBCs, their amplitude and location. These features have been here augmented by descriptors of the average relative powers of EEG rhythms, which were indeed reliable indicators of the severity of the pathology (with larger low frequency contributions associated to higher severity, as already found in other pathologies [27][36]). The same data considered in [38] were further investigated to see if the inclusion of information on EEG rhythms improved the identification of the correct severity. Indeed, classification performances largely increased and the best classifier included as input features the relative average power of alpha and theta rhythms in the 2 s before the SBCs, together with the number of SBCs in the frontal region.
Notice that the average power of the rhythms was similar in a time interval of a few seconds before and after the SBC. The seconds before the onset were chosen only to exclude the SBC, which has characteristic low frequency contributions that could bias the relative contributions of the rhythms. Specifically, we noticed that in a short time interval in which a SBC appears the slower rhythms are relatively more important than in the entire EEG trace. Thus, a slowdown of the activity was observed before and after an SBC and this slowing was larger when the severity of the pathology was greater.

As mentioned above, the classification performances are largely improved with respect to the previous method proposed in [38], showing that the EEG rhythms are important indicators of the severity of the encephalitis (primarily in the channel and in the time period around which an SBC appears). The performance is quite stable when considering the error of the classification model trained on the entire dataset or the performances of a leave-one-out test. The predictive value is over the 70% and the 80% when considering a 5- and 3-level severity classification, respectively. This performance can be considered high enough to provide a useful support to the diagnosis of encephalitis, mainly

in emergency settings or during a follow-up of the patient, in which invasive and time-consuming examinations are usually avoided.

General clinical assessment of the patient was not standardized (indeed, this is a retrospective study). Thus, some data (e.g., level of consciousness and body temperature) were not available for all medical examinations in which EEG traces were acquired. These data will be acquired in future prospective studies as their inclusion as input features could further improve the estimation of the severity of encephalitis.

Further studies are needed to assess other interesting properties of the SBCs. For example, their sources could be investigated, by estimating their locations [17][18], which could be then correlated with the lesions found in neuroimages (some promising results were obtained recently [56]). Deepening the study of SBCs could also be of help in improving their identification by adding some a-priori constraints to the processing algorithm. Moreover, additional features related to the severity of the pathology could be found and fed to a classifier to improve further the classification performance. As a further interesting future study, different pathological brain inflammations showing SBCs (e.g., HIV [7][8], Rasmussen's syndrome [10][14][24][25][33], West syndrome [15][50]) could be investigated, to understand if specific properties of this marker may be used to discriminate them.

5 Conclusion

Encephalitis should be diagnosed rapidly, but clinical assessment usually relies on either subjective evaluations or invasive and expensive examinations. An accurate and objective electrophysiological assessment could be a valid support for a rapid diagnosis and follow-up of patients. The slow biphasic complex (SBC) and the EEG rhythms (mainly in time windows close to SBC appearance) are reliable markers of encephalitis. Their automated identification allows to remove clinical subjectivity in EEG trace interpretation. Moreover, the classifier here developed using this information allows to assess the severity of the pathology. The method is non-invasive, economic and fast, thus providing an interesting support to the clinical examination. This promising result will be further tested in the future in different clinical settings.

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Luca Mesin graduated in Electronics Engineering in 1999 and received the Ph.D. in Applied Mathematics in 2003 from Politecnico di Torino, Italy. From 2003 to 2008 he was a Fellow of the Laboratory for Neuromuscular System Engineering of the Department of Electronics, Politecnico di Torino. Since 2008, he is Assistant Professor in Biomedical Engineering at the Department of Electronics and Telecommunications and head of the Mathematical Biology and Physiology group (Politecnico di Torino). His main research activities are in the fields of biomedical image/signal processing and mathematical modelling.

Massimo Valerio graduated in Medicine and Surgery in 2011 and obtained his specialization in Child Neuropsychiatry in 2017, at the University of Turin. He is currently a PhD student in Bioengineering and Medical-Surgical Sciences and works at the Department of Medical Science, University of Turin. His research interests are Neurosurgery, Neuroradiology and Neurology in Chilhood and Adolescence.

Giorgio Capizzi is a Medical Doctor expert in Neuropsychiatry in Chilhood. He has been director of the Italian League for Epilepsy and of a ward of Neuropsychiatry in the Regina Margherita Children's Hospital, Turin. He has been Associate Professor at the Department of Child Neuropsychiatry, Universitá di Torino, Turin, Italy. His main research interests are in the field of Child Neurophysiology.