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STUDYING EPILEPTIC ACTIVITY PROPAGATION: FROM ROBUST BUT TIME-CONSUMING TO INTELLIGENT INFORMATION PROCESSING METHODOLOGIES

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Abstract: *In this study intelligent biomedical information processing techniques are used in tracking epileptic activity propagation in patients with epilepsy. Although identification and detection of epileptic signatures from epileptic signals is also important and well managed by such techniques, reasons are given herein, that discuss why the above is not the most important issue in this field, but rather is the study of the propagation and development of epileptic activity itself. In this context, Independent Component Analysis (ICA) is utilised to study averaged epileptic signals from temporal lobe epileptics. The results are compared to those previously obtained by Magnetic Field Tomography (MFT) methodologies, and important findings are verified. Finally, the prospect of obtaining such sets of findings in a more intelligent and automatic methodology, so that they may, in future, become a blind procedure is discussed.*

Keywords: *Magnetic Field Tomography (MFT), Magnetoencephalography (MEG), Independent Component Analysis (ICA), neural networks, epilepsy*

1. INTRODUCTION

A key issue in biomedical information processing (a subdomain of medical informatics) is how to utilise the enormous content of the various recordings in an efficient and robust way. As technological/industrial advances provide the opportunity to obtain more data more frequently, the question is whether methodologies capable of exploiting this rich data content are becoming available as well, or not. The field of epilepsy, and neurophysiological recording and imaging of epileptic activity in specific, is one of those areas. Contemporary equipment facilitate the availability of millisecond by millisecond data

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from an epileptic head for spatial grids of less than a centimetre. Do modern epileptologists, however, feel they are in an advantageous position? The role of medical informatics in the above game is to equip the medical experts with robust methodologies capable of analysing the data in an efficient, time saving, but also intelligent way.

In the past, we have developed methodologies to analyse data recordings from epileptic patients. Those methodologies were based both signal and image processing techniques, and utilised a source modelling method, namely Magnetic Field Tomography (MFT) [1], that enabled three dimensional distributions of current rather than electromagnetic point dipoles only. Although information previously unavailable with other techniques was revealed, the whole procedure suffered from efficiency in time, and automation. In other words, it was a very time consuming process, and relevantly user unfriendly, in the sense that only non medical experts (mostly scientists) could make use of them. The aim of the current work, was, therefore, to exploit the vast potential of new intelligent techniques and methodologies, that would enable a more blind study of epileptic data, while at the same time maintaining the robustness of the procedures. To achieve the latter, data analysis was powered with newly developed intelligent techniques, namely, those incorporating independent component analysis (ICA), and a few of the previously obtained results were verified again from another perspective.

In the following, the area of neurophysiological studies in epilepsy is introduced and the contribution of intelligent techniques up to date is highlighted. An account of the most important findings with the MFT methodologies is then given, together with the justification of the shift of interest to the study of propagation rather than feature detection. The notion of ICA is then introduced, and the algorithms involved are presented in short. The latter are finally applied in the case of patients with epilepsy, and the results obtained are discussed in the light of the previous findings with MFT alone.

2. METHODS

2.1. *MEG/EEG Epilepsy studies*

Two of the basic techniques used in the study of epileptic activity, are Electroencephalography (EEG) and Magnetoencephalography (MEG). In this section, some general definitions regarding epilepsy and its study with EEG and MEG are given, followed by a short report on the contribution that neural networks have offered in this field, and more specifically on the problems of detecting and classifying epileptiform events. Then, the method of Magnetic Field Tomography (MFT) is introduced, and past findings are summarised. Finally, the role that new information processing techniques may play is challenged.

2.1.1. *General definitions*

Epilepsy is a syndrome of episodic brain dysfunction characterised by recurrent unpredictable spontaneous seizures [2]. In epilepsy studies, the time interval of a seizure is referred to as ictal, while that between seizures as interictal. During the latter intervals, epileptic discharges are also continued, but they may only be very short lasting (e.g. a few milliseconds long) and, therefore, not lead to any symptoms. Such discharges make themselves evident through the appearance of certain signal waveforms with various characteristics. Examples of such waveforms are the so-called spikes, or sharp waves, or spike and wave complexes. Therefore, tracking interictal epileptic signatures, necessitates the involvement of techniques that maintain in general a very good temporal resolution, and more specifically at the millisecond level.

Multichannel EEG and MEG are the only neurophysiological, non-invasive techniques that can follow the temporal sequences of such events. The former one, EEG, allows the study of brain activity by measuring the resulting electric potentials on the scalp by means of multiple electrodes, while the latter one, MEG, is concerned with the measurement of minute magnetic fields of a region of neurons outside the human skull by using multiple non-contact sensors.

2.1.2. *The use of artificial Neural Networks in epilepsy*

Although work in the field of neurophysiology drove the design of artificial neural networks early enough [3], it is only in the last decade or so that different types of neural networks (NNs) have been designed and shown to have practical applications with improved performances over more conventional approaches. As neural networks are capable of generalising consistent

features of patterns in the training sets, a methodology similar to that usually followed by neurophysiology experts in everyday practice, makes the use of computer simulations with neural networks an attractive tool for automated pattern recognition of epileptiform EEG/MEG activity [4]. Moreover, the latter case is made even more attractive by the fact that it is not necessary to devise a trained network generally appropriate for all cases, but only specific ones capable of representing features of the specific epileptogenic disorder for each patient examined.

2.1.3. *Epileptiform detection and Classification of epileptiform events*

Although to date, pattern recognition has remained one of the most difficult problems in EEG analysis, several reports about automatic detection in epilepsy have appeared in the past few years [5, 6, 7]. In most of these reports present methods of EEG analysis using neural nets for the recognition and quantification of various EEG epileptic patterns. For instance, Rummelhart and McClelland [8] developed a 3-layer neural net that permitted the discovery of non-linear relationships between complex input and output data. Their inputs propagated through their network in a feed-forward fashion, while back-propagation was used to minimise the output error by altering the weights between the layers by a non-linear least square algorithm. More recently, Jando et al [9] and Gabor and Seyal [4] designed and trained a back-propagation networks for recognising spike-and-wave patterns of inbred rat strains and interictal human recordings respectively.

It may also be possible to construct a set of neural networks, each of which may be trained to recognise only one type of epileptiform event, as well as, "normal" events, i.e. events with epileptic morphology (spiky, sharp and fast) but not epileptogenic (associated with epileptic discharges). In this way one may construct a system receiving the exits from N such kinds of neural networks, each one regarding the possibility of occurrence of a particular event, and correlate them subsequently with other important aspects of each epilepsy type (e.g. which channels presented the events), as well as, details of the patient's clinical history (patient age, symptoms etc). Data and information relating to certain types of epilepsy may be coded and presented in a rule based structure (IF-THEN-ELSE), and use fuzzy variables to quantify the data [10]. This may facilitate decisions taken by the rules to be processed and decoded, and finally suggested by the system to the responsible physician (e.g. "possible_paroxism", "possible_fit") in order to aid diagnosis.

2.1.4. *Studying the epileptic activity propagation*

What is even more interesting than epileptic signal (spikes, sharp waves etc) detection itself, is the tracking of epileptic activity propagation, as well as, the study of its properties and patterns. This is so because, most of the currently available treatment strategies for epileptic patients, depend upon details, such as, the degree of expansion of the epileptic region, the exact location of the area that initiates the "firing", thereby irritating and exciting the rest of the brain regions as well, and of course, the "route" that the epileptic activity follows inside the brain.

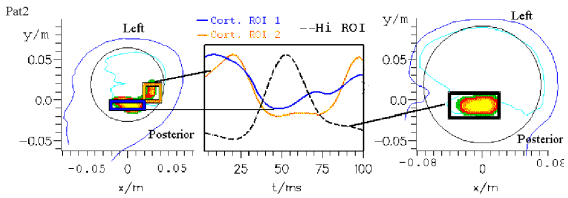

Fig.1. Left: superficial integrals of brain intensity over some 100 ms, (results from back-averaging 18 single event solutions of strong hippocampal activation, cf [14]. Two main ROIs are revealed in the sagittal view: one fronto-infero-temporal and one more posterior in the temporo-parietal region. Middle: graph of activations of the cortical and hippocampal ROIs. Note the pre- and post-hippocampal activation of the cortex. Right: sagittal view of deep intensity integrals.

In the past seven years, the feasibility of analysing unaveraged interictal MEG data with a robust method of MEG data analysis, namely, Magnetic Field Tomography (MFT) [1] was exploited [11]. During these studies, we were able to report unique observations concerning the spatio-temporal evolution of such activity [12]. During the development of a spike for instance, we identified that activity at the brain region called hippocampus both preceded and followed by a well-defined activity at the superficial brain structures (cortical activity), as shown in Figure 1 [13]. For the patients examined, the MFT analysis concluded that three regions were playing the most important role in the development of the interictal activity

per se. As it was unclear, however, whether these cortical to deep temporal interactions were noise artefacts or reflected true epileptic events, further processing was employed to verify the observations [14].

Most of the above work, however, was by no means automated, and therefore, required a substantial amount of time to be spent on just looking at the data (both signals and images).

2.1.5. *The role of ICA*

What is made obvious from the previous paragraph, is the need to utilise more automatic and if possible "blind" methodologies in the analysis of such data. Would it be possible, however, to exploit the aforementioned intelligent techniques in the study of epileptic activity propagation? In other words, could one make use of tools like the Independent Component Analysis in order to realise how many brain sources are contributing to the initiation and development of an interictal epileptic signal, and what is their relevant topographic arrangement? In the following sections, we shall demonstrate that it is actually feasible to use ICA for such a task.

2.2. *Blind Source Separation (BSS) and Independent Component Analysis (ICA)*

The field of Blind Source Separation (BSS) has recently been established as a basic research field not only within statistical signal processing, but within unsupervised neural learning as well. In this section, some general principles regarding BSS and ICA are given, followed by a short report on the main differences of ICA and PCA. Then, various ICA algorithms are described in brief, with special focus on those associated with the JADE technique and factor analysis, which are the ones used to obtain the results of this paper.

2.2.1. *BSS in general*

The main objective of BSS is to extract statistically independent sources from their (linear) mixtures with unknown mixing coefficients. As the exact number of independent components is usually unknown one may assume that this number is equal to the number of input channels. This is, however, an unstable assumption in the case of biosignals, since the number of independent components is usually much less than the total number of recording channels. Thus, certain mathematical techniques of independent component estimation have recently been developed based on multivariant statistical analysis, or neural networks.technique and factor analysis, which are the ones used to obtain the results of this paper.

So, consider a vector $\mathbf{x}=[x_1(t),...x_n(t)]^T$ with n mixtures of m independent sources $\mathbf{s}=[s_1(t), ...s_m(t)]^T$, where $n \neq m$, in general. The only initially available information that exists is vector x(t), which may be given in matrix form as:

$$\mathbf{x} = \mathbf{A} \cdot \mathbf{s} + \mathrm{n} \tag{1}$$

Matrix **A** is called the mixing matrix, while n denotes the noisy component. So, the solution to the problem of blind separation lies with the estimation of the elements of **A**, which are the mixing coefficients. As a consequence, **A** contains all the information associated with the mixing process. It should be noted at this point that:

1. The independent sources $s_i(t)$ are considered a stationary, zero mean, stochastic process $\{s_i(t)\}$.
2. The independent sources are mutually independent
3. Matrix **A** consists a linear transformation **A** = **x**$\rightarrow$**s.**

One of the most widespread techniques to implement BSS stems from Principal Component Analysis and is frequently used as a data decorrelation method in multivariate analysis, namely Independent Component Analysis (ICA). ICA assumes that a multivariate timeseries (or a stochastic process, in general) may be decomposed into some statistically independent timeseries called independent components. The goal is to extract from the original timeseries the independent timeseries, as well as, their mixing process.

The observed or recorded and generally mixed signals x form the input to the ICA technique, while the estimate, **y**=ŝ, of the independent components consists the ICA output. The demixing matrix W (the inverse or pseudoinverse of A) may also be considered as an output, since **y=Wx** (see Fig. 2 below).

2.2.2. *ICA versus PCA*

Both ICA and PCA consist linear transformations of two spaces, the space of signals and the space of components. PCA aims to extract the principal components, which are not correlated with each other. So PCA provides those data projections along which the variance is maximised. The principal components are orthogonal to each other and are sorted along the descend of the variance (the first PC is the one with the largest variance, and, therefore, the most uncorrelated component).

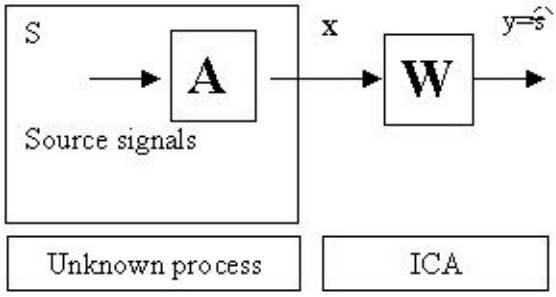

Fig.2. The general principle of ICA.

On the other hand, the independent components are not necessarily orthogonal (see Fig. 3). It may also be said that PCA uses second order statistics, while ICA uses higher order statistical correlations.

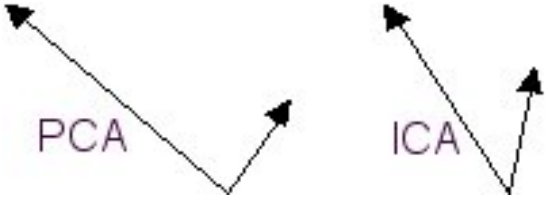

Fig.3. The difference between the PCA and ICA data projections.

2.2.3. *Algorithms for ICA*

The ICA idea may be implemented in various ways. Some of the most well known approaches found in the literature have to do with:

1. Minimisation of higher order moments – kyrtosis [15].
2. Minimisation of higher order cumulants [16].
3. Minimisation of the mutual information of the input [17].

Minimisation of the Kullback/Leibler divergence of the common pdf and the product of isolated pdfs of the output [18].

ICA can typically be implemented by two kinds of algorithms: off-line and on-line algorithms. The former ones make use of linear algebra methods and recursive expressions, while the latter ones use neural networks.

The off-line approach uses two basic steps [19, 20]:

(i) decorrelation or whitening, where the covariance matrix of the input signals is made diagonal so as to decorrelate the inputs as much as possible (PCA may also be used here), and

(ii) rotation, where the effect of high order statistics is minimised, so that input signals become as independent as possible. So we may say that, signal processing with ICA follows a pre-processing step, that may often be accomplished with PCA.

2.2.4. *ICA implementation using NNs*

As already mentioned in the neural networks section, there is usually a cost function that is optimised following a certain algorithm. Thus, the ICA method is generally characterised by relation [21]:

ICAMethod=CostFunct.+OptimiseAlgorithm (2)

The properties and the qualities of the ICA depend upon the choice of the cost function (e.g. one-unit cost function, multi-unit cost function, log-likelihood, mutual information and others) and the optimisation algorithm.

2.2.5. *Kinds of on-line ICA with NNs*

What remains once the cost function is chosen, is the optimisation algorithm that is going to be utilised. Some of the algorithms that have been reported in literature are the following (details of these may be found in [22, 23, 18].

1) Heuralt-Jutten Algorithm, based on the zeroing of the non-diagonal elements of the covariance matrix.
2) The EASI algorithm (similar to the previous, but avoiding the inversion of **W** (Figure 1).
3) Bell-Sejnowski algorithm (BS) and its extension (ExtBS).
4) Natural Gradient algorithm (ACY, WACY)
5) Fixed Point algorithms (FP, FastICA).

It needs to be mentioned here that all the above algorithms neglect the effect of noise on data modelling. Recently, however, some newly developed algorithms have shed light on this matter, by attempting to limit the noise effect during the pre-processing/whitening step during the application of PCA. Nonetheless, the problem of dynamically dealing with noise remains to be solved.

Finally, and according to Giannakopoulos et al [24] one may develop criteria (indices/metrics) that may be used to measure the efficiency of each algorithm. By trying the above algorithms on different sets of data (MEG data as well) it was found that the FP/FastICA and the ExtBS algorithms perform efficiently enough.

2.2.6. *The JADE algorithm*

One of the most well known off-line algorithms is the so called JADE (Joint Approximate Diagonalisation of Eigenmatrices, [16], which consists of two basic stages. In the first stage, the covariance matrix is calculated and then from it the decorrelation/whitening matrix is also calculated. By mutliplying the input data with the decorrelation matrix the data become as decorrelated as possible. This stage is usually implemented using PCA or Factor Analysis (see below).

The second stage consists of a search for a rotation matrix, which jointly diagonalises the eigenmatrices obtained from the fourth order cumulants of the already decorrelated data. That is, fourth order statistics are used in this stage via the cumulants [19].

A brief list of the algorithmic steps of JADE is as follows:

1) The covariance matrix, **R**, of the input matrix is formed.
2) From **R**, we calculate the matrix **W** (whitening), that diagonalises **R**.
3) The cumulants z(t)=**W**x(t) are calculated, and they are represented by their equivalent eigenmatrices.
4) With the joint diagonalisation of the above eigenmatrices, which satisfies a certain criterion (maximises a certain expression), the rotation matrix **U** is obtained.

The demixing matrix is then **B**=**UW**, and the independent components are obtained via s(t)=**B**x(t).

2.2.7. *Factor Analysis*

In many cases, like EEG and MEG, the existence of noise in the data limits in a large degree the ability of the PCA technique during the pre-processing phase, that aims to render the data as uncorrelated as possible. In addition, the number of independent components is unknown. It is because of these two reasons, that the PCA phase is abandoned, and Factor Analysis (FA) is used instead. In FA, the number of components/sources is estimated according to a certain statistical criterion, but the additive noise is also considered and taken out of the independent components [25].

By altering the notation in equation (1) slightly, we obtain (3):

$$\mathbf{x}=\mathbf{A}\cdot\mathbf{f}+e \quad (3)$$

where s (independent components) has now been replaced by f (factors), with $\mathbf{f} \sim N(O,I_m)$ (a diagonal matrix with a normal distribution of elements), and n has been replaced by $\mathbf{e} \sim N(O,\Sigma)$, where Σ_{nxn} a diagonal matrix of the noise covariance. In (3), **f** and **e** are considered to be mutually independent, and x has zero mean.

There are generally two approaches in implementing FA. One of them is called principal factor analysis (based on PCA), while the other is called maximum likelihood estimation (MLE). In brief though, FA's goal is threefold:

(i) estimate m, the number of parameters or else independent components/sources.
(ii) estimate **A**, the factor loading matrix (factor mixing)
(iii) estimate $\mathbf{\Sigma}$ in (3).

The estimation of $\mathbf{\Sigma}$ and **A** may be done (in the case of MLE) using the expectation maximisation algorithm [26] and in order to be facilitated m must satisfy a certain condition. The estimation of m in turn, is based on the number of eigenvalues of the covariance matrix (PCA like criteria). By sorting the eigenvalues in descending order, a threshold is introduced according to a condition, and m is chosen so that it satisfies the threshold. Another technique is the so called Minimum Descriptive Length (MDL) criterion which uses MLE itself as an estimator [25].

In summary, **A** and **Σ** are estimated for various m values and the set (m, **A**, **Σ**) that satisfies the MDL estimator is chosen. The basic difference of FA and PCA is that FA rejects noise through the estimation of **Σ**.

Finally, if **Q** is the pseudo-inverse of **A** (**AQA**=**A**) as obtained by FA, then z=**Q**x. The independent components are obtained by (4):

$$S=\mathbf{B}z=\mathbf{BQ}x \quad (4)$$

where Q is obtained from FA, and B is obtained from ICA. From a theoretical point of view, the algorithm FA+JADE does not reject the additive noise as such, but it rather projects the data from a space of dimension n, to a space of dimension m, with m<n, by using a linear transformation **BQ** in such a way as to compress the noise e into lower dimensions.

3. MATERIAL

3.1. *Signal description and sensor topology*

The MEG recordings were made with the 37-channel SIEMENS KRENIKON system that contained first-order axial gradiometers coupled to DC-SQUIDs. All measurements were made within a magnetically shielded room. The patient lay comfortably on a couch, with her head locked into a stereotactic frame. The plane of sensors was centred over, and parallel to, the left temporal area of the brain during the recordings. The whole sensor/patient set up is illustrated below in Fig. 4.

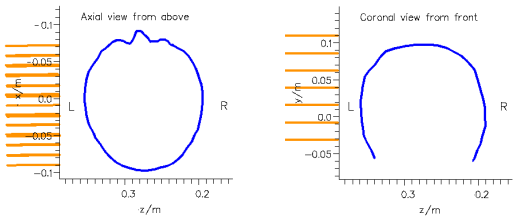

Fig.4. The MEG sensor set up over the patient's head..

The data were band-pass filtered on-line through 0.5–70.0 Hz, digitised at 0.4 kHz. A spatio-temporal cross-correlation matching technique [27] was also applied on the digitally filtered (1.5–47.5 Hz) and heart artifact corrected data [28] to identify and align single epileptic events (spikes and sharp waves) for averaging. The length of the template events chosen varied from 142 ms to 217.5 ms, but pre- and post-template data segments were included in the process resulting in an average signal of 2000 ms. The averaging process including the template selection with some of the data details are illustrated in Fig. 5.

3.2. *Patient histories*

Three patients (two males, one female) suffering with pharmaco-resistant Complex Partial Epilepsy (CPE), with ages from 18 to 42 years old, were included in the study. CPE onset ages varied from 14 to 20 years of age. Common symptoms included daily seizures of dizziness, impaired consciousness, acoustic sensations like noise, dominating later on; and frequent seizure generalisations.

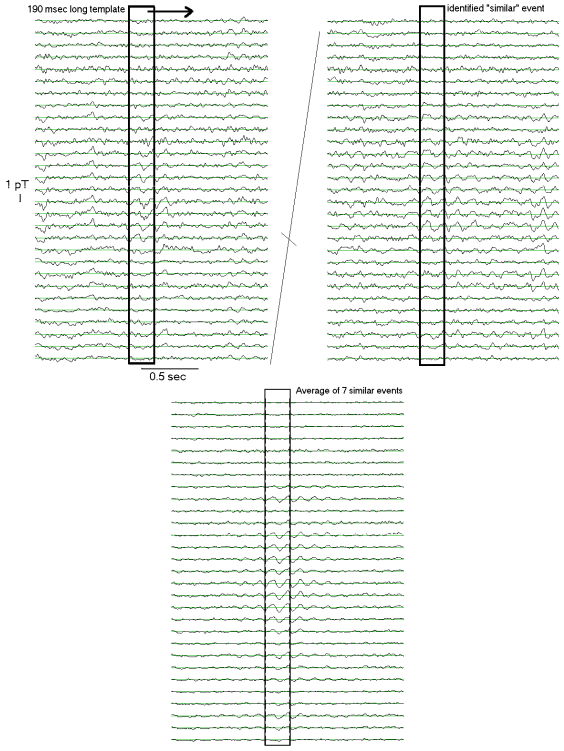

Fig.5. The epileptic event averaging process.

4. RESULTS

Consider the signal illustrated in Fig. 6, that represents an epileptic spike as identified by an epilepsy expert. The epoch consists of 800 timeslices (covering a total period of 2.0 secs), with the spike being centred around the 400th timeslice.

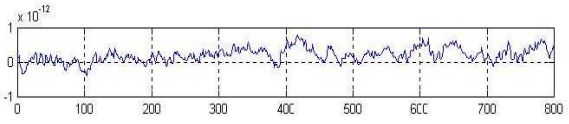

Fig.6. An identified epileptic spike (one channel shown only, raw signal).

Suppose the averaging procedure as outlined in the previous section is performed on the above signal, which results in the averaged signal shown in fig: 7.

The question imposed is to identify the number of components that contribute to the appearance and the development of the spike, as well as, the importance of each component at specific time periods (like the ones marked by vertical lines in Fig. 7 for example).

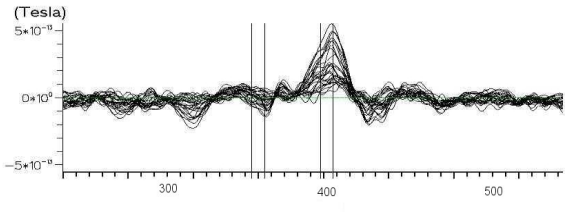

Fig.7. Signal obtained from averaging 10 "similar" and aligned interictal epileptic events (spikes). Some thirty channels are superimposed on top of each other. Vertical lines are for demonstration purposes only, see text.

If we execute the algorithm FA+MDL we get an estimate on the possible number of the components being present. By so doing, we obtain the indication that there are five independent components in the data. Doubling this number (in order to avoid generality limitations) and simply running the FA+JADE algorithm for ten (10) independent components we obtain the results shown in Fig. 8.

It may be easily noticed now that the first three independent components of the above result seem to be the most interesting ones, as the provide information about the central part of the signal, that is the spike (around timeslice 400 in the figure), while most of the rest ones contain a lot of information about processes occurring away from the spike peak, as well as, a good deal of background noise. Figure 8 also points out that there is a certain order of activation for the first three independent components: IC2 becomes activated first, IC1 follows, and finally IC3 appears, always with respect to the neighbourhood of timeslice 400.

This result supports in a certain extend verifies the information previously obtained with the MFT studies, that revealed ordered interactions between the (deep) hippocampal area with (superficial) cortical regions (see section 0). On this basis, it would be interesting to see the topographic appearance of each component or else a rough localisation of them. This may be done by first plotting the contribution of each input channel to each independent component in a column chart (see Fig. 9), by using the values of each column of the mixing matrix **A** (equations 1,3). Combining this information then, with the sensor topology of the experimental set up (Fig. 10), and after performing a two dimensional interpolation, gives a rough estimate of the localisation of the independent components (Fig. 11).

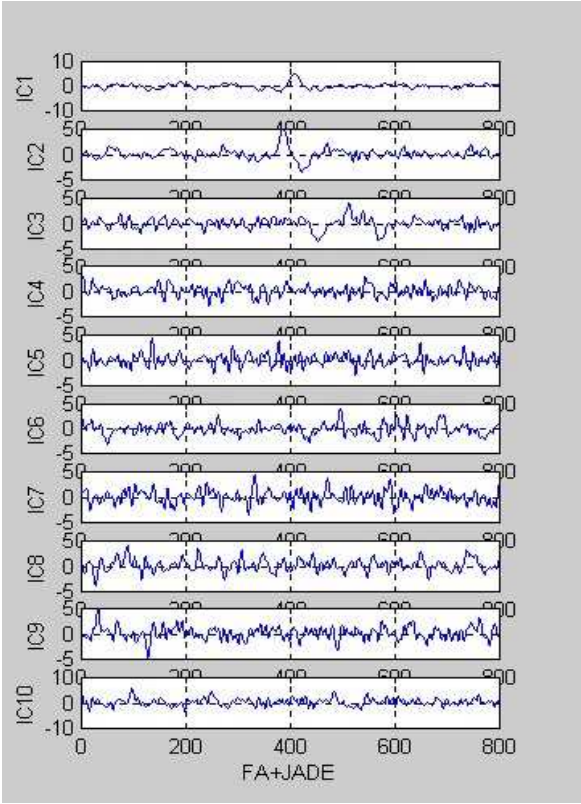

Fig.8. Independent components obtained with the FA+JADE algorithm.

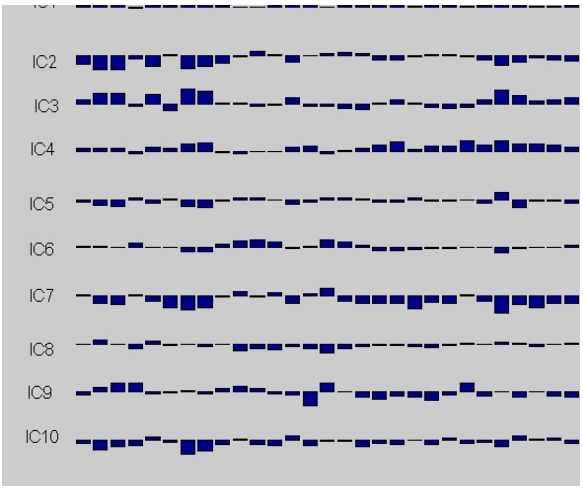

Fig.9. Column chart of the mixing matrix coefficients. Each column corresponds to an input channel and consequently to an element of the mixing matrix A. A convention is used for the sign of each value/column, and therefore, only relevant comparisons are valid.

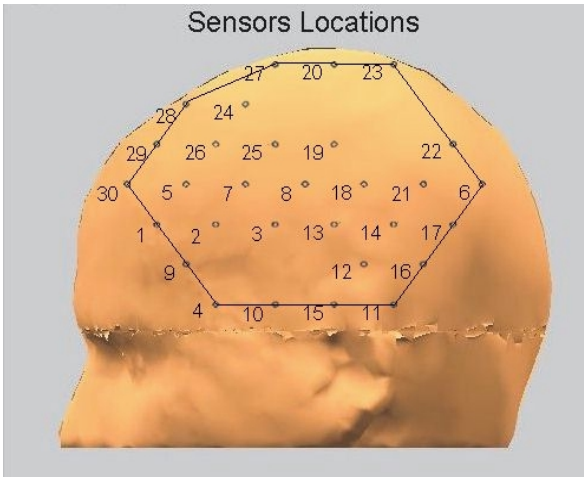

Fig.10. Sensor locations with respect to patient head.

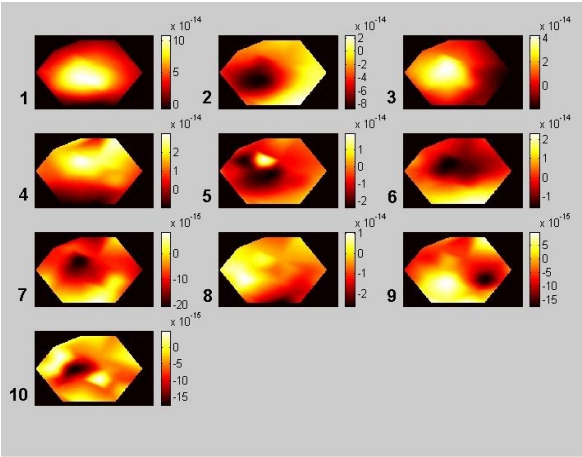

Fig.11. A rough localisation of each independent component.

5. CONCLUSION

In this study intelligent biomedical information processing techniques were used in tracking epileptic activity propagation in patients with temporal lobe epilepsy. Although in the past, a vast majority of researchers focused their studies in identifying epileptic signatures from signals of such patients, contemporary research and everyday clinical practice have demanded extra information. In this report, reasons were given to justify why epilepsy detection itself is not the most important issue in this field, but rather is the study of the propagation and development of epileptic activity itself.

In this context, newly developed methods and algorithms described by the theory of ICA were used to verify previously obtained results in a more intelligent and automatic methodology. More specifically, the JADE algorithm was used (with FA and MDL) to verify results previously obtained by MFT methodologies. Although this paper presents results from one epileptic patient the study has been conducted in data from another two similar patients, and similar results were obtained.

The above combination allowed for a generally automated process like ICA to contribute to a previously very time consuming procedure. The results obtained with MFT were the product of not only long calculations, but also intensive observation, mostly done in a manual fashion, with small glimpses of automation and intelligence. ICA offers the possibility to fully automate the above procedure, and facilitate the "blind" usage of the technique by non-science experts, especially when coupled with a user friendly interface.

Although it is fairly early to judge the full details of the methodology we have followed, this study certainly shows the potential hidden in the exploitation of these techniques. Further work needs to be done, however, to allow for the study of single epoch/event signals, and also reveal the relationship between the average and the raw signals as well. The importance of the findings lies both within the general agreement with clinical observations, as well as, the agreement of two completely independent techniques and/or methodologies, and, therefore, cannot be underestimated.

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