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# Complex network analysis of human ECoG data

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ABSTRACT

Localization of the epileptogenic zone (EZ) is an important issue in epileptology, even though there is not a unique definition of the epileptic focus. By using complex network analysis of electrocorticographic (ECoG) data we identify three singular areas in the temporal lobe of epileptic patients, the node with highest local synchronization power, the most connected node, and the node with highest interactions load. Connectivity in the data is extracted from the Minimum Spanning Tree (MST) of global correlations. We address the question whether removal of these nodes during the surgery is crucial in the suppression or reduction in the quantity of post-operative seizures. From five ECoG records, local areas with high synchronization power appear to be significantly involved in the development of epileptic seizures. The other two areas seem not to be fundamental in the seizures onset and development. Moreover, the approach proposed shed new light in cortical connectivity patterns in the human temporal lobe. All the analyzed records are during the inter-ictal state.



Epilepsy is a neurological disorder characterized by recurrent seizures. In particular, focal epilepsy refers to those epilepsies where the cortical zone, named epileptogenic zone (EZ) or focus, responsible for the seizures can be localized. If the patient's focus can be well localized and he/she is reluctant to drug therapy (as it is approximately 30% of the epileptic population), the patient is a candidate to respective surgery [1,2]. In both focal and generalized seizures, defining and localizing the EZ in human epilepsy is still an open issue [2]. Two main zones are directly related with the EZ, the ictal onset zone (OZ) and the irritative zone (IZ). During the seizures or *ictal state*, the OZ is the specific location in the brain where synchronous activity of neighbouring groups of cells becomes so strong to be able to spread its own activity to other distant regions. When this global and synchronous activity is established throughout large areas in the cerebral cortex several pathological conditions will appear in the epileptic patient. Symptoms like convulsions and loss of consciousness are most often the result of this abnormal brain activity.

In between seizures, during the *inter-ictal state*, epileptogenic signatures in the form of spikes can sometimes be identified and tracked in the electroencephalogram (EEG) and electrocorticogram (ECoG). Intraoperative ECoG is performed during the surgery using a grid of electrodes placed directly over the brain cortex and employed as a last resort in order to improve the focus' localization. When a specific and well determined area, the IZ, is identified as the source of epileptogenic spikes, serious clues regarding the EZ location can be advanced during the inter-ictal state, even though the ictal phase is still the primary source for localization. Two main limitations however play against the use of spike analysis through ECoG recordings. It is well known [3] that the IZ showing inter-ictal spikes not always contains the EZ, misleading therefore the guided surgery. Moreover, anesthesia [4] can suppress (halothane, nitrous oxide, propofol) or activate (enflurane and etomidate) spikes, confounding the analysis. These two facts are included into the many reasons why in some cases of surgically operated patients where the suspected focus has been removed, recurrent seizures appear [1,2,5]. This conventional analysis thus requires a revision in order to better characterize and localize the epileptic focus.

New approaches has been developed in the last years in order to uncover the underlying cortical dynamics whether in the normal [6–9] or in the epileptic brain [10–14] and thus characterize in a reliable way the cortical areas responsible for the seizures. In accordance with the literature [3], we shall show here that no single area seems to be involved in the seizures, but there exist two kinds of sites with apparently different but fundamental roles in the crisis development. Our conclusions are extracted from the analysis of ECoG data [11,13,14] and during the inter-ictal stage. The last point is important due to the impossibility to reliably predict epileptic seizures with more than a few minutes [6].

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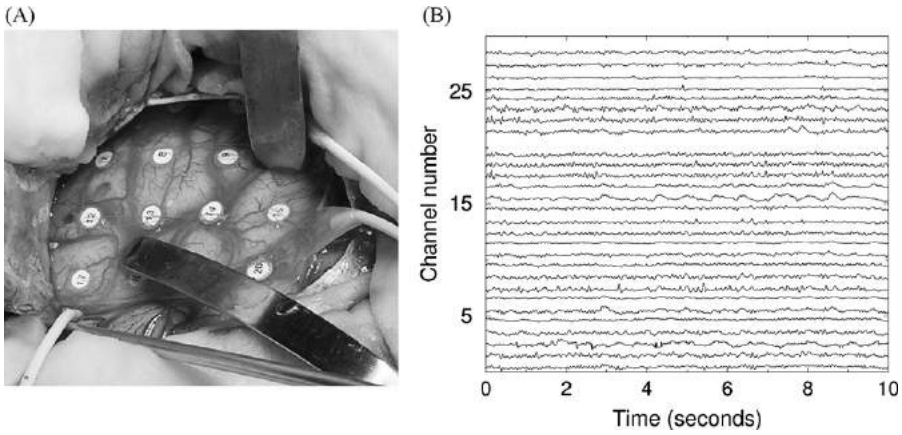


**Fig. 1.** Electrocortigraphy. (A) Electrodes grid over the temporal cortex and the inner strip only seen by its connectors in the left-lower part of the photograph. (B) 10 s of raw data. Channels 1 to 20 corresponds to the 4 × 5 grid and channels 21 to 28 to the inner strip.

We have showed very recently [15] that removal of critical sites in the lateral temporal cortex in epileptic patient results in no further seizures, at least when the critical nodes are unambiguously identified. These results came from a purely local analysis. In the present work we use complex network tools in order to dig further into the functional connectivity in the temporal cortex of epileptic patients. Data provided by using this methodology constitutes additional information which could improve our understanding of the temporal lobe epilepsy.

ECoG recordings obtained from five patients were analyzed. A grid of 4 × 5 electrodes is placed over the external part of the temporal lobe (lateral temporal cortex) and a strip of eight electrodes is placed into the mesial part of the temporal lobe (through the Sylvian fissure). In this way, electrical activity at both sides of the lobe is registered. Interelectrode distance is 1 cm. Fig. 1(A) shows the 4 × 5 grid during the recording process and the electrodes strip only seen by its connectors in the left-lower part of the photograph.

In order to quantify the interactions between pairs of electrodes' time series, we have calculated the Pearson correlation coefficient [16] between electrodes $i$ and $j$

$$\rho_{ij} = \frac{\sum_{k=1}^{N_{win}} (x_i(k) - \bar{x}_i)(x_j(k) - \bar{x}_j)}{\sqrt{\sum_{k=1}^{N_{win}} (x_i(k) - \bar{x}_i)^2 \sum_{k=1}^{N_{win}} (x_j(k) - \bar{x}_j)^2}} \quad (1)$$

where $\bar{x}_i$ is the mean value of channel $i$ in the period considered. Windows of $N_{win} = 1024$ data points sampled at 200 Hz (5.2 s) has been analyzed. A final correlation matrix is obtained after typically averaging 32 non-overlapping windows. Fig. 1 shows the ECoG setup (A) and a typical record (B). Fig. 2(A) shows the correlation matrix corresponding to Fig. 1. No other synchronization measures have been used in this analysis. As showed in [15] other nonlinear statistics like phase synchronization and mutual information yields similar results.

Local interactions in the electrodes grid were estimated by averaging correlations between each channel $i$ with its first neighbours,

$$s_i = \frac{1}{n_i} \sum_{j=1}^{n_i} \rho_{ij} \quad (2)$$

where $n_i$ is the number of first neighbours of electrode $i$ (3, 5, or 8) in the 4 × 5 grid (see [7,17] for a similar definition, although it is now normalized by the electrode connectivity). This "on-the-grid" representation of intra-lateral interactions gives an idea on the contribution of each cortical area to *local* synchronous activity. We shall call synchronization power of channel $i$ the value given by $s_i$ and local critical node (LCN) the channel with the highest value of $s_i$. Fig. 2 display both the correlation matrix (A) and the representation of local interactions (B).

A common procedure to uncover functional connectivity between different brain areas is by using thresholds in the correlation matrix $\rho_{ij}$ [7–9], which however introduces the uncertainty in the threshold value to be selected. We adopt here a different procedure based upon the Minimum Spanning Tree (MST) [18,19] construction which produces a unique network structure. From the correlation matrix $\rho_{ij}$ which is a dissimilarity measure, we compute a similarity measure by calculating the "distance" between two electrodes time series. Following Gower [20] we define the distance between the time evolution of channels $i$ and $j$ as,

$$d(i,j) = \sqrt{\rho_{ii} + \rho_{jj} - 2\rho_{ij}} = \sqrt{2(1 - \rho_{ij})} \quad (3)$$

The last equality comes from the symmetry property of the correlation matrix, $\rho_{ij} = \rho_{ji}$ and the normalization $\rho_{ii} = 1$ for every channel $i$. The MST, constructed from a set of $N$ elements, 28 in our case, endowed with distances $d(i,j)$ between every pair of elements $i$ and $j$, is a planar graph with $N-1$ edges connecting the $N$ elements and minimum total length, *i.e.* $\sum_{\text{in the MST}} d(i,j)$ is a minimum respect to whatever other tree. The illustrative way to understand the construction of the MST is by ordering pairs by distances in ascending order and adding elements to the tree as they appear in the list. No loops exist in the MST. The MST displays only the most important links in each node.

Once a functional connectivity tree is constructed, one can take advantage of the powerful tools developed in the last years around the complex networks theory [7,8,17,21–23]. From a *global* interactions point of view, two particular nodes seem to be relevant in regard to interactions in the temporal lobe. One of them is the most connected node, that is, the node with the highest number of links. We shall call this node the Global Critical Node 1 (GCN1). The other one is the node with highest "load" in the tree, which is calculated through the *node betweenness* [21]. Node betweenness is one of the standard measures of node centrality, because it is directly related with the importance of a node as being part of the path between whatever other two nodes. We shall call this the Global Critical Node 2 (GCN2).

Fig. 3 shows three typical MST constructions. In this case, we have used the information provided by the 4 × 5 grid and the eight electrodes inner strip (see above). Electrodes 1 to 20 are in the grid

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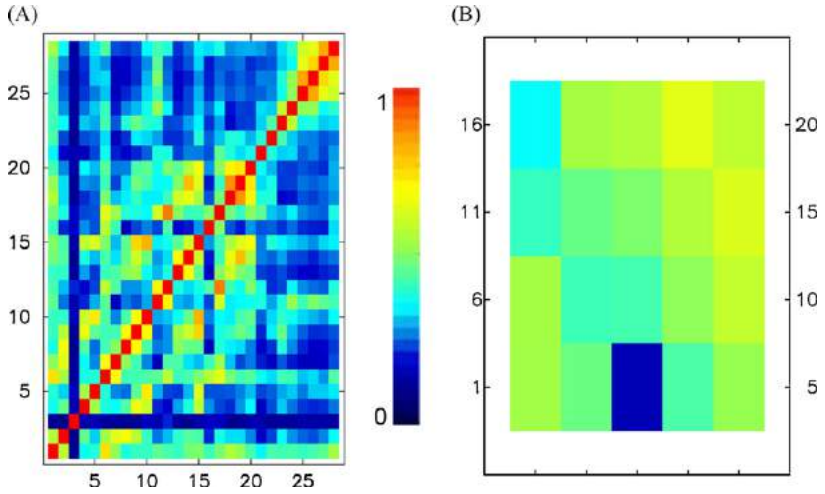


**Fig. 2.** (A) Correlation matrix of 28 electrodes in the ECoG of Fig. 1(B). (B) "On-the-grid" representation of intra-lateral interactions (Eq. (2)).

(white circles) and electrodes 21 to 28 belong to the strip (gray circles).

By using Eq. (2) we have estimated the local synchronous activity over the lateral temporal cortex in human epileptic patients. For every patient the maximum intensity in each pattern has also been identified. For instance, in Fig. 2(B) there is a clear intensity cluster at the upper-right part of the grid, in electrodes 15, 19 and 20. Maximum is located at electrode 19. This is the LCN.

Global analysis, on the other side, proceeds as explained above. From the correlation $\rho_{ij}$ matrix one obtain the corresponding distance matrix $d(i,j)$ and then the MST is constructed, as in Fig. 3. The MST in Fig. 3(A) corresponds to the ECoG of Figs. 1 and 2. Besides the local links between neighbour's sites, as for example in $i$ and $i$+1 or $i$ and $i-5$ there exist also long range (or "small-world" [21–23]) links. It is possible to identify in Fig. 3(A) three non-neighbouring links, 6–16 and 6–17 and the link of electrode 3 with electrode 12. This last link however must be considered with caution because the artifactual character of the channel 3, as can be seen also in the raw data of Fig. 1 and also in the grid representation of Fig. 2. There exist however a particular site which is different from the rest and it is the electrode 6 (yellow circle with red border) in Fig. 3(A)). This location is the most connected node in the set and it is also the node with the highest interactions load. Its character as a GCN2 can be readily understood regarding its location into the MST. Moreover, it has most of the different kind of links, long-range and local. Note that the critical node 6 is different from the LCN 19 (cyan circle). The first one, even though is highly and globally connected does not have the local synchronization power of the second one.

Fig. 3(B) displays another case where the three critical nodes are in different positions, although very close from each other. Moreover, there exist two GCN1, namely electrodes 3 and 12. The central role played by the GCN2 it is readily apparent in this MST, with fewer connections than the GCN1 but in a more involved position.

Lastly, Fig. 3(C) displays the particular case where the three critical nodes match at the same position in electrode 2 (magenta circle with red border).

In order to follow the role played by these nodes, we have analyzed five patients suffering from focal epilepsy who underwent respective surgery at the Hospital La Princesa (Spain). Informed consent and approval by the local ethic committee were always obtained. In every case an intraoperative ECoG analysis has been carried out previous to the resection procedure. In each patient's ECoG data, LCN, GCN1 and GCN2 have been identified. We then checked whether the critical nodes have been extracted during the surgery. Table 1 shows the results along with other relevant information. Surgical outcomes were evaluated using the detailed Engel's scheme [5]. According to this classification an Engel IA corresponds to completely seizure free, whereas other classifications state for different frequency of post-surgical seizures (a year following the surgery). The surgery success is rather independent of the number of channels, i.e. tissue extent, extracted, as can be readily concluded by comparing #EC and Engel columns. There remain seizures even in the case of large portion of lobe extracted, as for example in patients 3 or 4. On the other hand, the case with minor number of channels extracted, patients 1 were free of seizures after a year following the surgery.

One can infer from Table 1 that extraction of the LCN seems to be a *sufficient* condition for the eradication of seizures after de surgery, that is, excision of the LCN *implies* absence of post-operative seizures. When LCN is excised, post-operative seizures disappear, as the case of patients 1 and 2. On the other side, no extraction of LCN does not imply however that seizures will remain after the surgery, but it is likely that this happens (two cases out of three). Take for example the cases of patients 1 and 4. MST of patient 1 is displayed in Fig. 3(C)., where the three critical nodes match at the same position in channel 2. In this case little tissue extent has been extracted during the surgery, the tissue encompassing channels 1, 2 and 3, but with very high "effectiveness" because the patient remained without seizures after a year following the surgery. On the other hand, patient 4 has suffered post-operative seizures even after large quantities of cortical tissues have been removed. In this last case the LCN has not been removed, like cases of patients 3 and 5 as well. In these three cases the LCN has not been removed and in some cases the global critical nodes has been removed or not. Even though seizures frequencies has been reduced in patients 3 and 4 (both are Engel IIB) which imply an improvement in the epileptic condition, there remain seizures after the surgery. From the three cases where the LCN has not been removed, that is patients 3, 4 and 5, two of them remained with post-operative seizures, but patient 5 remained free of them. However this patient has suffered from some post-operative "auras" without seizures, immediately following the surgery. This is a remarkable fact taking into account that auras are the first stage in the seizure development due to the electrical activity of the seizure focus [2]. This kind of facts could shed light regarding the particular role played by each of the critical nodes in the seizure development. This study is currently under way.

As displayed in Table 1, in four of the five cases the origin of the epileptogenic activity is in the mesial part of the temporal lobe, as it is demonstrated by the video-EEG (scalp + foramen

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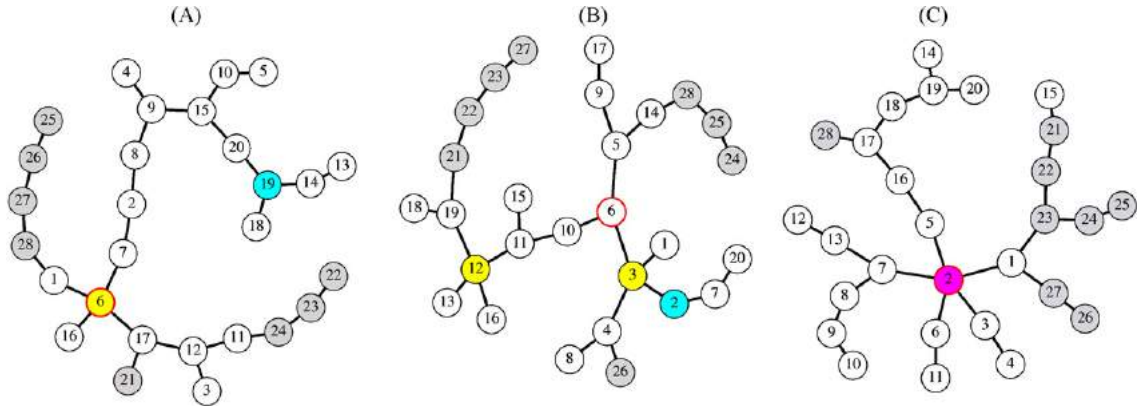


**Fig. 3.** Minimum Spanning Tree and critical nodes: electrodes' grid is represented by electrodes 1–20 (white circles). Electrodes' strip is represented by electrodes 21–28 (gray circles). LCN is represented by a cyan circle, GCN1 by a yellow circle and GCN2 by a red-border circle. Magenta circle represents superposition of LCN and GCN1. (A) MST of the same ECoG data of Figs. 1 and 2, corresponding to patient 3 in Table 1. GCN1 and GCN2 are superimposed (channel 6) and distant from the LCN (channel 19). (B) Another case (patient 2 in Table 1) where the three critical nodes are in different position and there exists two GCN1. (C) In this case (patient 1 in Table 1) the three critical nodes are located at the same position (channel 2).

**Table 1**
Removal of critical nodes and crises after the surgery.

| | LCN | GCN1 | GCN2 | #EC | Seizures | RMN | v_EEG | Surgery | Engel |
|---|---|---|---|---|---|---|---|---|---|
| 1 | Yes | Yes | Yes | 3 | Partial complex | Normal | R Mes | R AMTR | IA |
| 2 | Yes | No | Yess | 4 | Partial complex | Bi-T MS (R > L) | R Mes | R AMTR | IA |
| 3 | No | Yes | Yes | 9 | Partial complex | R hippo atrophy | L Mes | L AMTR | IIB |
| 4 | No | No | Yes | 10 | Partial complex | R MS | R Mes | R AMTR | IIB |
| 5 | No | Yes | No | 12 | Partial complex | Normal | R Lat | R AMTR | IA |

Yes: critical node has been removed; No: critical node has not been removed. Hippo: hippocampus; Bi: bilateral; Lat: lateral; Mes: mesial; MS: mesial sclerosis; L: left; R: right; T: temporal; AMTR: anterior medial temporal resection. #EC: number of extracted channels during the surgery.

ovale electrodes) studies. In patient #5 the origin is in the lateral region of the temporal lobe. Network analysis on the other hand, locates critical nodes in the lateral cortex in the five patients. This apparent disagreement is explained by the very different kind of information both methods yields. Video-EEG and also traditional ECoG analysis are focused mainly in epileptogenic signals, whether ictal or inter-ictal, in the form of spike activity. Network analysis on the other hand, records continuous interactions showing up functional connectivity maps in the temporal cortex. Whether epileptogenic activity follows functional connectivity patterns is a question of great interest which could not be answered with this solely analysis. In the first place, inter-ictal epileptogenic activity could be misleading as pointed out above. In second place, ictal activity is difficult to obtain during intraoperative ECoG analysis.

Summing up, functional connectivity in the temporal cortex can be extracted from ECoG data through the use of the MST and critical areas can also be exposed by using complex network methodologies. Regarding the functional connectivity, the graphical construction used in this Letter allows to uncover not only intra-lateral interactions in the temporal lobe, but also intra-mesial and lateral-mesial interactions as well. This fact would be important in the case a direct comparison against samples of respected hippocampus wants to be performed. Intra-mesial and lateral-mesial connectivity can be compared against normal and sclerosed hippocampus samples, a far reaching task beyond the scope of the present work. On the other side we were able to identified two kinds of critical spots in the temporal lobe related with the interactions ranges. Highly local correlations are characterized by the LCN. On the other side global interactions are characterized by the GCN1 and the GCN2. The information provided by this methodology is highly interesting and valuable. On the one side, ECoG serves as a zoom to explore cortical and mesial dynamics, an issue unavailable with conventional EEG. On the other side, an extension of network analysis to ictal states should complement the functional connectivity patterns found in the inter-ictal states and, more important, could shed new light regarding the actual paths followed by the epileptogenic activity. However, intraoperative ictal ECoG records are hard to be obtained.

Much more research is necessary to develop and apply in a confidently way this methodology in the benefit of the epileptic patient, but this kind of work would open new insights in the use of current devises. For instance, even though our analysis is based on ECoG data, which requires an intra-operative procedure, it would be possible to extend this kind of study to non-invasive recordings like MEG or high resolution multi-channel EEG. If this kind of analysis would yield similar results as exposed in this letter, it would be possible to explore new non-invasive therapeutic procedures in the focal epilepsy. For example, cases like patient 5 displayed in Fig. 3(C) would be treated with gamma-knife surgery, with no need for a surgical incision.

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