**Dear Editor, below you will find our answers to the Editor and Reviewers comments/concerns. Comments from reviewer #1 were copied down from the pdf document. Suggested changes made by both reviewers and the Editor were done using the track control. Our answers (in bold face) follow each editor/reviewer comment. In some cases however, we found some conflicts in accepting the reviewers’ requests and, at the same time, follow the JoVE instructions for authors. In those cases, a compromise solution was implemented.**

**Answers to Editorial comments:**

The manuscript has been modified by the Science Editor to comply with the JoVE formatting standard. Please maintain the current formatting throughout the manuscript. The updated manuscript (54746\_R2\_042516.docx) is located in your Editorial Manager account. In the revised PDF submission, there is a hyperlink for downloading the .docx file. Please download the .docx file and use this updated version for any future revisions.  
  
1. Additional detail is required:  
-2.3 – How is fluoroscopic imaging performed? Please provide a citation.

**A reference has been provided in the text**

**Zampella, J.E., Brown, A.J., Azmi, H. Percutaneous techniques for trigeminal Neuralgia. In: Handbook of Stereotactic and Functional Neurosurgery. Gandhi D.C., Schulder, M. ed., Chapter: 34, doi: 10.1201/9780203912416.ch34 (2003).**

-3.2.1 – How are the distances measured and marked?  
-3.2.3 – How is the circumference created?  
-3.2.4 – Are electrodes placed at these positions? Or are marks made? Please specify.

**The Information required in these points is now included in the text**

-3.6 – How are the areas located? How are they recorded? More detail is required for this step to be filmed?

**This information is now included the text. During the film the head model will be seen in the computer screen.**

-Will the scripts/codes used be provided as supplemental files?

**The scripts used in most of the calculations are home-made and hardly illustrative, at least without a step-by-step and extensive explanation. Therefore, we provide a table with the R functions employed and explained.**

-4.5, 5.1.2 – Please provide a citation or the code as a supplemental file.

**See above**  
  
2. Results:  
-Please re-write the results section so that the figures are cited within the text [ie (Figure X)] with discussion of the data rather than formatting it as “Figure X shows…”. This reads too much like a list of figure legends.  
-Figures 3 & 4– Please label the y-axis.

**This section has been rewritten according with the reviewer suggestion**

**Answers to** Reviewer #1:

Note to reviewers: **In some cases we found some conflicts in accepting the reviewers’ requests and, at the same time, follow the JoVE instructions for authors. In those cases, a compromise solution was implemented.**

1- (line 75) Very vague remarks...only in focal epilepsies especially TLE,surgery becomes a viable option...make adequate changes

**The paragraph was modified according with the reviewer suggestion**

2- (line 75) Surgical outcome needs to be commented a range quoting all important outcome studies in TLE after surgery.A single value of 66% is not acceptable.

**The paragraph was modified according with the reviewer suggestion and a new reference (3) was included.**

3- (line 83) Network hypothesis with references needs to be highlighted since this manuscript is dependent on the same.

**A new paragraph with 5 new relevant references (5-9) has been included in this new version of the manuscript, following the reviewer suggestion.**

4- (line 94) Although a time tested procedure,is FOE still in use and if so,is it being routinely used in any center?

**FOE are routinely used in our center as part of the protocol in some drug resistant TLE patients. FOE are actively used in other medical centers, see for instance reference:**

**Sheth, S. A., Aronson, J. P., Shafi, M. M., Phillips, H., Velez‐Ruiz, N., Walcott B.P., Kwon, C.S., Mian, M.K., Dykstra, A.R., Cole, A., Eskandar, E.N. (2014). Utility of foramen ovale electrodes in mesial temporal lobe epilepsy. *Epilepsia*, *55*(5), 713-724.**

5- (line 130) Why certain areas are highlighted yellow?

**Yellow areas will be included in the script of the film. They represent key issues of the work. It is an editorial request.**

6- (line 238) Has this methodology utilized eralier?

**Yes, the methodology showed in this work has been used in several earlier works, on either FOE or subdural electrodes, for instance:**

**Vega-Zelaya et al. Assessing the equivalence between etomidate and seizure network dynamics in temporal lobe epilepsy. Clin Neurophysiol. (2016) 127(1):169-78.**

**Vega-Zelaya et al. Disrupted Ipsilateral Network Connectivity in Temporal Lobe Epilepsy. PLoS One. 2015 Oct 21;10(10):e0140859**

**Vega-Zelaya et al. Inhomogeneous cortical synchronization and partial epileptic seizures. Front Neurol. 2014 Sep 24;5:187.**

**Ortega et al. Impaired mesial synchronization in temporal lobe epilepsy. Clin Neurophysiol. 2011 Jun;122(6):1106-16.**

**Also, other groups (on neurophysiological recordings) utilized network approaches:**

**Courtens et al. Graph Measures of Node Strength for Characterizing Preictal Synchrony in Partial Epilepsy Brain Connect. 2016 Jul 22.**

**van Diessen et al. Electroencephalography based functional networks in newly diagnosed childhood epilepsies. Clin Neurophysiol. 2016 Jun;127(6):2325-32.**

**Burns et al. Network dynamics of the brain and influence of the epileptic seizure onset zone. Proc Natl Acad Sci U S A. 2014 Dec 9;111(49):E5321-30.**

**van Diessen et al. Brain Network Organization in Focal Epilepsy: A Systematic Review and Meta-Analysis. PLoS One. 2014 Dec 10;9(12):e114606.**

**Varotto et al. Epileptogenic networks of type II focal cortical dysplasia: a stereo-EEG study. Neuroimage. 2012 Jul 2;61(3):591-8.**

**Wilke et al. Graph analysis of epileptogenic networks in human partial epilepsy. Epilepsia. 2011 Jan;52(1):84-93.**

**Schindler et al. Evolving functional network properties and synchronizability during human epileptic seizures. Chaos. 2008 Sep;18(3):033119.**

**Ponten et al. Small-world networks and epilepsy: graph theoretical analysis of intracerebrally recorded mesial temporal lobe seizures. Clin Neurophysiol. 2007 Apr;118(4):918-27.**

**This methodology has been the subject of several reviews:**

**Bernhardt et al. Network analysis for a network disorder: The emerging role of graph theory in the study of epilepsy. Epilepsy Behav. 2015 Sep;50:162-70.**

**Gleichgerrcht et al. Connectomics and graph theory analyses: Novel insights into network abnormalities in epilepsy.** [**Epilepsia.**](http://www.ncbi.nlm.nih.gov/pubmed/?term=Gleichgerrcht+et+al+2015%2C+Epilepsia) **2015 Nov;56(11):1660-8.**

**van Diessen et al. Functional and structural brain networks in epilepsy: what have we learned? Epilepsia. 2013 Nov;54(11):1855-65.**

**Rubinov and Sporns Complex network measures of brain connectivity: uses and interpretations. Neuroimage. 2010 Sep;52(3):1059-69.**

**Boccaletti, S., Latora, V., Moreno, Y., Chavez, M., Hwang, D-U. Complex networks: Structure and dynamics. Phys Rep. 2006 424, 175-308.**

**Sporns et al. Organization, development and function of complex brain networks. Trends Cogn Sci. 2004 Sep;8(9):418-25.**

**And also, it has been used on fMRI data, for instance in:**

**Pereira et al. Asymmetrical hippocampal connectivity in mesial temporal lobe epilepsy: evidence from resting state fMRI. BMC Neurosci. 2010 Jun 2;11:66.**

**Bettus et al. Decreased basal fMRI functional connectivity in epileptogenic networks and contralateral compensatory mechanisms. Hum Brain Mapp. 2009 May;30(5):1580-91.**

7- (line 242) If epochs containing artefacts are excluded,won't the seizure onset of most seizures need to be eliminated because of the chewing and movement artefacts so common in TLE?

**As expressed in the main text of the manuscript, no artifacts were present in the analyzed recordings. Those recordings with artifacts, including muscle artifacts, were automatically discarded.**

8- (line 321) No details on how many patients or seizures were included in analysis. What are the inclusion and exclusion criteria or do all the patients undergo the same if they are TLe?

**The results presented here are representative results from only one patient. The aim of the manuscript is a methodological one. In this sense, number of patients and/or seizures and therefore the inclusion and exclusion criteria do not apply. These variables, however, can be consulted in the manuscript’s bibliography, over which the described methodology is grounded.**

9- (line 394) Such redundant statements can be avoided since they do not add anything to this study,,non-traditional points of view...means????

**According with the reviewer suggestion, this paragraph has been deleted.**

10- (line 409) Include the authors' new innovations which has come up from this study in detail rather than a rambling discussion on what is to be done and what not?

**The inclusion of methodological steps into the Discussion section is an explicit requirement stated in the Instruction for authors of JoVE. In any case, a whole new paragraph was introduced (Discussion) regarding the innovations presented in the manuscript, as suggested by the reviewer: “The application of the technique …”**

11- (line 417) What has this experiment added to the already existing armementarium of tools in presurgical evaluation of TLE other than a routine FOE needs to be highlighted

**A new paragraph was introduced in the Discussion highlighting the importance of network over traditional analysis over FOE recordings: “This result could not be anticipated …”**

12- (line 432) Explain how it substantiates or refutes the network theory?

**See above (points 10 and 12)**

13- (page 14) ?? Legend to figures

**Legends of figures were in lines 358-380 (former version).**

14- (page 14) Figure B do not add anything

**Figure B has been changed**

15- (page 14) Figures are very poor quality

**Figures quality has been improved (300x300dpi) in this new version of the manuscript.**

*Major Concerns:*  
N/A  
*Minor Concerns:*  
N/A  
*Additional Comments to Authors:*  
N/A

Answers to Reviewer #2:

Note to reviewers: **In some cases we found some conflicts in accepting the reviewers’ requests and, at the same time, follow the JoVE instructions for authors. In those cases, a compromise solution was implemented.**

*Manuscript Summary:*  
In this study, authors combined a traditional clinical protocol with a mathematically-sounded network analysis methodology to study the origin and propagation of epileptiform-like activity in the brain of epileptic patients. The paper is well-organized and discusses an interesting growing research area in clinical neuroscience, i.e. "the concept of pathological brain networks". I have some major comments that need to be address in order to recommend this paper for publication in JoVE.  
  
*Major Concerns:*  
1- Quality of figures is bad. Figure 1A need to present clearly the location for FOE as well as well define anatomical landmarks. The head of the patient with all electrode sets should be magnified in Figure 2B. Please, select attractive segments with EIDs and ictal data for Figure 1C. Please, indicate each of them and also provide their equivalent EEG segments. Provide the original data for the segment in Figure 2.

**According with the reviewer suggestion we have improved the quality of figures, specifically: The upper part of Figure 1A has been replaced by two MRI displaying the FOE contacts (white arrow heads). In the lower part of Figure 1A the exact location of FOE contacts are displayed in a human anatomical specimen. Figure 2B shows now the head of the patient right after the insertion surgery (left panel) and during the video-EEG room stay. Figure 1C has been replaced by the original video-EEG recordings corresponding to Figure 2.**

**Besides that, the resolution of all the figures has been increased up to 300x300dpi.**   
  
2- Is section 4.2 needed?  
**Actually, it depends on the software employed to export data from the acquisition equipment and also the software employed to preprocess it. In any case, we explain the procedure as detailed as possible during this critical step.**

3- Purpose of 4.5 is unclear. Please, explain it

**Point 4.5 has been eliminated in this new version of the manuscript because does not add any significant information.**

4- Provide Schindler's equations in 5.1.1, as well as frequency range and Shannon's equation in 5.1.2

**Schindler's and Shannon’s equations have been added to the supplemental file. Frequency ranges have been add to the text.**

5- Functional connectivity at the level of sensor has been currently criticized by the community. Most of researches recommend performing it at the level of the brain sources. Please, explain why authors are using a sensor based analysis.  
**Although reconstruction of brain sources (from electrodes recording activity) is tempting in some ways, it entails several difficulties. The first one, and perhaps the most important is the lack of a unique model of the reconstructed source space. Moreover, any suitable model is, to some extent, arbitrary. While we are certainly aware of the problems of inferring interactions from scalp electrodes locations, specifically due to volume conduction, we prefer to circumvent this issue by using measures of synchronization which avoids this kind of contamination, as for instance the phase synchronization (also known as Phase Locking Value). A new paragraph was introduced in this new version of the manuscript mentioning this important issue (Discussion section).**

6- Please provide a rationale for the selection of the window parameters in 5.3.

**The whole paragraph was rewritten. There is no underlying criterion in the selection of these parameters.**

7- The note in line 325 - Is this the only criterion for good recording condition? I found it very inaccurate.

**Of course the criteria employed to ensure a correct implantation and good recording conditions are much more involved that the one expressed in a simplified phrase used former version of the manuscript. In order to avoid misunderstandings, we have eliminated this phrase from the manuscript.**

8- The note-like conclusion in line 350 should be removed since the authors only show the data for a single patient.

**The conclusion from line 350 has been deleted.**

9- Lack of discussion about the results from the network analysis. This is the main objective of this paper, so it has to be discussed and compared with other groups doing the same analysis in epilepsy. Based on the above obtained network, I would like to see a discussion whether a decrease in the weight of the edges or a rupture of edges or a change in the topology of the network are driving the triggering of the seizure. It would be very helpful to translate the methodology into a guidance for surgeons. They computed most of the important network features by using the R software, however they do not provide values neither discuss among these features which one might be the best or worst predictor.

**Because the manuscript’s aim is a methodological one, we focus discussion on this particular issue, describing as detailed as possible all of the potential caveats one may encounter. In order to show the potential usefulness of the presented approach, we included a new paragraph summarizing some of the main results previously obtained by using this methodology. The cited bibliography in this new paragraph can be accessed for particular issues encompassed in the methodology.**

**Regarding the neurosurgeon issue requested by the reviewer, we have to mention that no surgery therapy is hypothetically envisioned by using this kind of analysis. However, a potential therapy using electrical stimulation could be implemented in order to balance the detected synchronization impairment. We have added a new sentence in this direction, according with the reviewer suggestion (“from a therapeutic point of view …”)**

10- I would like to see a schematic representation of the anatomical network obtained from this procedure for this particular patient, with an explicit mention with edges are carrying the largest weight in the obtained weighted network. A discussion about postsurgical results will be also required.

**A video Figure (Figure 5) has been added in order to show the dynamics of the anatomical functional connectivity during seizure. See the preceding point regarding post-surgical results.**

11- They mention a threshold value for the correlation coefficient (Pearson correlation between two time series) to be used as a mark to consider two areas connected; however I could not identify any value neither the justification of it. They just provided the procedure but missed the inclusion of values. At what level of statistical significance they are working is missed also.

**The threshold value applied in the particular case of the manuscript is stated now (Note of point 5.2.1). A threshold of 0.5 with (typically) 1000 points in each time series yields for the correlation a p-value less than < 0.00001. More involved details of thresholds and statistical significance can be consulted in the references, in particular:**

**Vega-Zelaya, L., Pastor, J., de Sola, R.G., Ortega, G.J. Disrupted Ipsilateral Network Connectivity in Temporal Lobe Epilepsy. *PLoS ONE* 10 (10), e0140859, doi: 10.1371/journal.pone.0140859 (2015).**

12- Regarding the point 3, it is common to use the Akaike Information Criterion along with the cross correlation coefficient in order to guarantee the validity of the "connected areas". I could not find any discussion about that.  
**No AIC was used because no linear regression models were used to calculate the Pearson coefficient between two different time series.**

*Minor Concerns:*  
1- Line 134 - for -> from  
2- Line 272 - five -> 5

**Both concerns have been solved.**

3- Regarding the bibliography, I would like to see references as the following:  
- Fundamentals of Brain Network Analysis, A. Fornito, A. Zalesky, and E. Bullmore, AP Press (2016)

- Concepts and principles in the analysis of brain networks, G.S. Wig, B.L. Schlaggar, and S.E. Petersen, Ann. N.Y. Acad. Sci. 1224 (2011) 126 - 146.  
- Complex network measures of brain connectivity: Uses and interpretations, M. Rubinov, O Sporns, Neuroimage 52 (2010) 1059 - 1069.  
**References have been added to the manuscript.**

4- Few references are from recent years, most of them are from before 2011. Only one from 2015 and couple from 2011 and one from 2012, the rest are from before 2010.  
**Recent references have been added.**  
  
*Additional Comments to Authors:*  
N/A