Seizure onset zone localization from many invasive EEG channels using directed functional connectivity

Pieter van Mierlo, Ana Coito, Serge Vulliémoz
Functional Brain Mapping Lab, EEG and Epilepsy Unit
Geneva University, Geneva University Hospital
Geneva, Switzerland
Pieter.vanMierlo@UGent.be

Octavian Lie
Department of Neurology
University of Texas Health Science Center of San Antonio
San Antonio, Texas, United States of America
Lie@uthscsa.edu

***Abstract*— In this study we investigated how directed functional connectivity can be used to localize the seizure onset zone (SOZ) from ictal intracranial EEG (iEEG) recordings. First, simulations were conducted to investigate the performance of two directed functional connectivity measures, the Adaptive Directed Transfer Function (ADTF) and the Adaptive Partial Directed Coherence (APDC), in combinations with two graph measures, the out-degree and the shortest path, to localize the SOZ. Afterwards the method was applied to the seizure of an epileptic patient, recorded with 113-channel iEEG and localization was compared with the subsequent resection that rendered the patient seizure free. We found both in simulations and in the patient data that the ADTF combined with the out-degree and shortest path resulted in correct SOZ localization. We can conclude that ADTF combined with out-degree or shortest path are most optimal to localize the SOZ from a high number of iEEG channels.**

Keywords—Seizure onset zone localization; directed functional connectivity, epilepsy, intracranial EEG

I. INTRODUCTION

Epilepsy is a neurological disorder characterized by the occurrence of spontaneous seizures that affects approximately 1% of the world population. Epilepsy is considered a network disorder, because multiple brain regions can be involved during a seizure [1]. The clinical symptoms of the seizure are related to which brain regions are involved. The brain region from where the seizure originates is called the seizure onset zone (SOZ) [2].

During the presurgical evaluation, the epileptogenic focus is localized and eventual overlap with eloquent brain tissue is assessed to decide the most optimal treatment for the patient [2]. Here, the most important medical investigations are video-EEG monitoring, MRI, interictal PET and ictal SPECT. In approximately 15-25% of patients that undergo presurgical evaluation, invasive EEG monitoring is necessary to gain valuable information about the SOZ and the spreading that is not clear from the non-invasive examinations [3]. During the invasive EEG monitoring electrical brain activity is recorded from depth electrodes or stereo EEG electrodes placed inside the brain's parenchyma and/or from subdural grids on top of the cortex. Which brain regions are targeted is decided based on the non-invasive examinations. Due to the rapid spreading of the epileptic seizure activity in the brain, it is a difficult task to identify the SOZ.

The visual interpretation of the intracranial EEG (iEEG) is the clinical standard for mapping focal seizures targeted by epilepsy surgery. However, it is labor-intensive and prone to localization errors due to interpreter dependency. Functional brain connectivity can help to localize the SOZ [4]. It estimates how brain regions functionally interact by investigating biomedical recordings such as EEG and functional MRI. Functional connectivity is defined as the study of temporal correlations between spatially distinct neurophysiological events [5].

Multivariate, parametric and frequency-based connectivity measures related to the concept of Granger-causality have been shown to map the SOZ with promising results [6, 7]. However, these methods have generally been applied to a limited number of iEEG channels/time series (<50-60), often selected based on visible involvement in the course of a seizure. This is because this analysis is normally very computationally intensive. Here, we tested whether connectivity estimates based on unselected complete iEEG time series from a high number of iEEG recordings can be useful for accurate SOZ mapping. Furthermore, we assess which connectivity measures in combination with which graph measures are the most suitable to localize the SOZ.

In the first part, simulations are performed to quantify the performance of the different connectivity measures in combination with graph measures. In the second part, ictal iEEG recordings from an epileptic patient are used to validate the performance of SOZ localization from a large number of channels using the different proposed measures.

II. METHODS

A. Seizure simulations

We simulated multiple seizures as recorded in 128-channel intracranial EEG. First, there are 2s of baseline activity after which the seizure starts in a randomly chosen channel, the simulated SOZ, and lasts for 3s. The seizure spreads from this channel to max 3 other randomly chosen channels (the propagated channels) with an onset delay between 1 and 250 ms and a sample delay of 1 to 5 samples. From the propagated channels the seizure spreads subsequently again to max 3 other channels until 32 channels participate in the seizure (1 SOZ channel + 31 propagated channels). The baseline activity is simulated as 1/f noise [8], while the seizure activity is a time-varying sinusoid starting at 12 Hz at the beginning of the

978-0-9928-6265-7/16/$31.00 ©2016 IEEE

seizure and 8 Hz at the end of the seizure. The signal-to-noise ratio (SNR) of the seizure activity compared to the baseline activity was -5, 0, 5 or 10db. We selected 32, 64, 96 or 128 of the 128 channels before SOZ localization to investigate the effect of increasing the number of electrodes. An overview of the simulation parameters can be found in table 1. An example of a simulated connectivity graph and corresponding seizure is shown in Fig. 1.

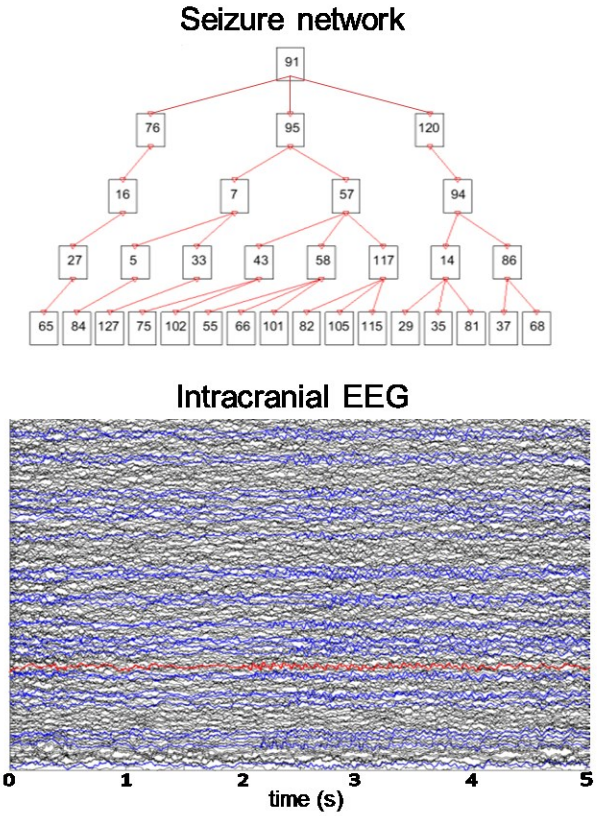

Fig. 1. Simulated ictal network and intracranial EEG recordings. In this example node 91 is the SOZ. The iEEG signal of the SOZ is depicted in red, while the signals of the nodes that are active during the seizure are in blue.

TABLE I. SEIZURE SIMULATION PARAMETERS

Parameters	Value
Sampling frequency	200Hz
Number of channels	128, 96, 64, 32
Number of ictal channels	32
Baseline duration	2 s
Seizure duration	3 s
Sample delay	Random (1 to 5 samples)
Onset delay	Random (1 to 250 ms)
Max number of propagated channels	3
SNR	-5,0, 5 and 10 dB
Seizure signal frequency	12 to 8 Hz
Number of simulations	320

B. Patient data

A 113-channel ictal iEEG epoch was analyzed from a patient who had undergone a right frontoparietal opercular resection at the University of Texas Health Science Center at San Antonio. The substrate of his epilepsy consisted of an MRI-positive focal cortical dysplasia type II b [9]. The patient has been seizure free at the last clinical follow-up 3 years postoperatively. This study has been approved by the local institutional ethics research board. Intracranial EEG was recorded with subdural grids and strips at 500Hz sampling frequency, and contained 5-sec preictal and 30-sec ictal activity identified by visual inspection of the epileptologist (OL). The implantation scheme is depicted in Fig. 2. An 8x8-contact inferior frontal grid (IFG, interelectrode distance: 5 mm) overlaid the lesion in the right perisylvian areas. An additional 2x5 superior frontal grid (interelectrode distance: 1 cm) and multiple strips were placed around IFG and interhemispherically. A 2-contact recording reference (G) was placed over the anterior mesial portion of the right superior frontal gyrus, removed from areas of high cortical irritability.

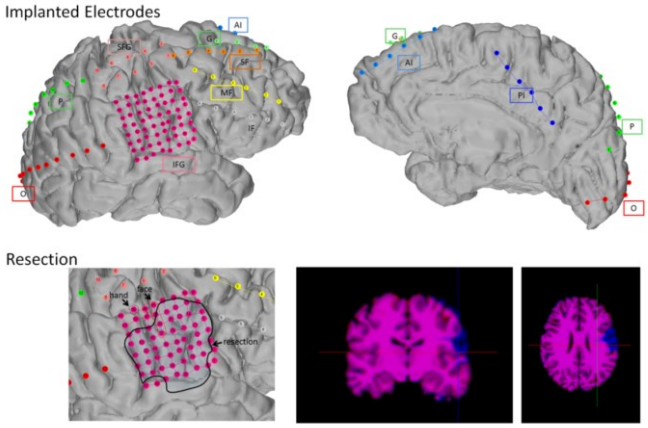

Fig. 2. (A) Electrode implantation scheme of the patient and (B) the resection that rendered the patient seizure free.

C. From intracranial EEG to seizure onset localization

1) Pre-processing

The patient data were low-pass filtered (0.5Hz to 45Hz) with a notch at 60 Hz and afterwards down sampled to 250Hz. Both the simulation and patient data were z-scored before performing functional connectivity analysis.

2) Time-varying functional connectivity

The functional connectivity measures we used in this paper are based on the concept of Granger causality. A signal x_1 is said to Granger-cause another signal x_2, when including the past of signal x_1 helps to better predict signal x_2 beyond when only the past of signal x_1 itself is included [10].

Autoregressive modeling is a commonly used technique to investigate the causality between signals. The pre-processed signals were modeled using a time-varying multivariate autoregressive (TVAR) model with an empirically chosen model order p equal to 5. The intracranial EEG is represented as a linear combination of its own past as follows:

$$\boldsymbol{X}(t) = \sum_{m=1}^{p} \boldsymbol{A}_m(t)\boldsymbol{X}(t-m) + \boldsymbol{E}(t) \quad (1)$$

Where $\mathbf{X}(t)$ is the iEEG signal matrix, $\mathbf{A}_m(t)$ is the model coefficients matrix for delay m and $\mathbf{E}(t)$ is the noise matrix. The coefficients of the TVAR model were estimated using a Kalman filter with update coefficient equal to 10^{-3} and Kalman

smoothing term equal to 100 [11]. To investigate the causality between the signals in the spectral domain the Fourier transform is applied to the coefficient matrices at each time point *t*.

$$\boldsymbol{A}(f,t) = \boldsymbol{I_K} - \sum_{m=1}^{p} \boldsymbol{A}_m(t) \exp\left(-i2\pi \frac{f}{f_s} m\right) \quad (2)$$

where $\mathbf{I_K}$ is the *K* times *K* identity matrix, with *K* the number of channels. The transfer matrix **H** is the inverse of the Fourier transform of the coefficient matrices.

$$\boldsymbol{H}(f,t) = \boldsymbol{A}(f,t)^{-1} \quad (3)$$

Based on different normalizations of **A**(f,t) and **H**(f,t) matrices, a number of multivariate directed functional connectivity measures are defined, such as the Adaptive Partial Directed Coherence (APDC) and the Adaptive Directed Transfer Function (ADTF):

$$APDC_{ij}(f,t) = \frac{|\boldsymbol{A}_{ij}(f,t)|^2}{\sum_{k=1}^{K} |\boldsymbol{A}_{ik}(f,t)|^2} \quad (4)$$

$$ADTF_{ij}(f,t) = \frac{|\boldsymbol{H}_{ij}(f,t)|^2}{\sum_{k=1}^{K} |\boldsymbol{H}_{ik}(f,t)|^2} \quad (5)$$

The integrated APDC and ADTF (iAPDC and iADTF) and the full-frequency APDC and ADTF (ffAPDC and ffADTF) are different normalizations of the APDC and ADTF over the frequency band of interest.

$$iAPDC_{ij}(t) = \frac{1}{f_2 - f_1} \sum_{f=f_1}^{f_2} \frac{|\boldsymbol{A}_{ij}(f,t)|^2}{\sum_{k=1}^{K} |\boldsymbol{A}_{ik}(f,t)|^2} \quad (6)$$

$$iADTF_{ij}(t) = \frac{1}{f_2 - f_1} \sum_{f=f_1}^{f_2} \frac{|\boldsymbol{H}_{ij}(f,t)|^2}{\sum_{k=1}^{K} |\boldsymbol{H}_{ik}(f,t)|^2} \quad (7)$$

$$ffAPDC_{ij}(t) = \sum_{f=f_1}^{f_2} \frac{|\boldsymbol{A}_{ij}(f,t)|^2}{\sum_{f'=f_1}^{f_2} \sum_{k=1}^{K} |\boldsymbol{A}_{ik}(f',t)|^2} \quad (8)$$

$$ffADTF_{ij}(t) = \sum_{f=f_1}^{f_2} \frac{|\boldsymbol{H}_{ij}(f,t)|^2}{\sum_{f'=f_1}^{f_2} \sum_{k=1}^{K} |\boldsymbol{H}_{ik}(f',t)|^2} \quad (9)$$

The iAPDC, iADTF, ffAPDC and ffADTF are normalized with respect to incoming information flow at each time point *t*. This means that the following normalization holds:

$$\sum_{j=1}^{K} iAPDC_{ij}(t) = 1 \quad (10)$$

The ADTF measures are able to reveal cascade connections, while the APDC measures reveal only the direct connections. Simply put, if there is a connection from x_1 to x_2 and from x_2 to x_3 at the same frequency *f* and time *t*, the APDC measures will find the connections x_1 to x_2 and x_2 to x_3, while the ADTF will find the connections x_1 to x_2 and x_1 to x_3. The ADTF shows the origin of information flow, while the APDC shows the direct connections.

3) Graph measures to localize the SOZ

Once the directed functional connectivity measures are calculated we use 2 methods to localize the SOZ: the out-degree and the shortest path. The out-degree looks at the number of out-going connections, while the shortest path calculates the shortest path between the electrodes. We use the summed out-degree (ω) and summed shortest path (ψ) to identify the SOZ:

$$\omega_j = \sum_{t=t_1}^{t_2} \sum_{k=1}^{K} conn_{kj}(t) \quad (11)$$

$$\varphi_j = \sum_{t=t_1}^{t_2} \sum_{k=1}^{K} \sigma_{kj}(t) \quad (12)$$

Where $conn_{kj}$ is the connectivity value (iADTF, ffADTF, iAPDC or ffAPDC) from signal x_j to signal x_k and σ_{kj} is the shortest path from node *j* to node *k* in the graph where the inverse of the connectivity values are used as weights of the edges. If there is a large connection from x_1 to x_2, the inverse is used as edge weight from x_1 to x_2, meaning that the cost of the edge will be less if the connectivity is higher. The node with the highest summed out-degree or the node with the lowest summed shortest path is identified as the SOZ.

D. Evaluation of the simulations

The simulations are evaluated based on two measures: area under the curve (AUC) and percentage correctly identified SOZ.

1) Area under the curve

The true positive (TP), false positive (FP), true negative (TN) and false negative (FN) connections of the simulations were assessed by comparing the thresholded time-varying connectivity matrix of each of the connectivity measures with the ground truth. For the APDC measures the direct edges of the simulation were considered as ground truth, while for the ADTF the cascade connections were considered as ground truth. We consider the complete threshold range 0 to 1 in steps of 0.01 to calculate the TP, FP, TN and FN. The AUC is calculated based on the sensitivity and the precision to assess the performance of the different connectivity measures.

2) Correct SOZ localization

The percentage of correctly localized SOZ in the simulations is calculated based on the summed out-degree and the summed shortest path. The nodes with the highest summed out-degree and lowest summed shortest path are compared to the simulated SOZ.

E. Evaluation of the patient data

The proposed methods to localize the SOZ are applied to the ictal intracranial EEG of the patient. To evaluate the influence of the number of channels on SOZ localization we selected three subsets of channels: (i) all 113 channels; (ii) the IFG grid that contains 64 channels and (iii) a 25 rectangular subset of the IFG grid with corners IFG9, IFG13, IFG41 and IFG45. The SOZ localization is compared with the resected region as depicted in Fig.2 and with the visual analysis of the epileptologist.

III. Results

A. Simulations

The results of the simulations are shown in Fig.3. Panel A shows the AUC values for the different connectivity measures, while panel B shows the percentage of correctly localized SOZ. The AUC of the ADTF values is higher than those of the APDC values. The integrated and full-frequency variants perform equally well. The more channels, the more the AUC drops. The AUC drops approximately 20% and 10% when comparing 32 with 128 channel ADTF and APDC analysis, respectively.

As can be clearly noticed in panel B, the ADTF measures are preferred for SOZ localization. The effect of the number of channels is limited. The out-degree and shortest path measure perform equally to localize the SOZ using the ADTF. The shortest path measure is the preferred graph measure to use in combination with the APDC connectivity to localize the SOZ when compared with the out-degree. An overall increase of approximately 40% is achieved in this case.

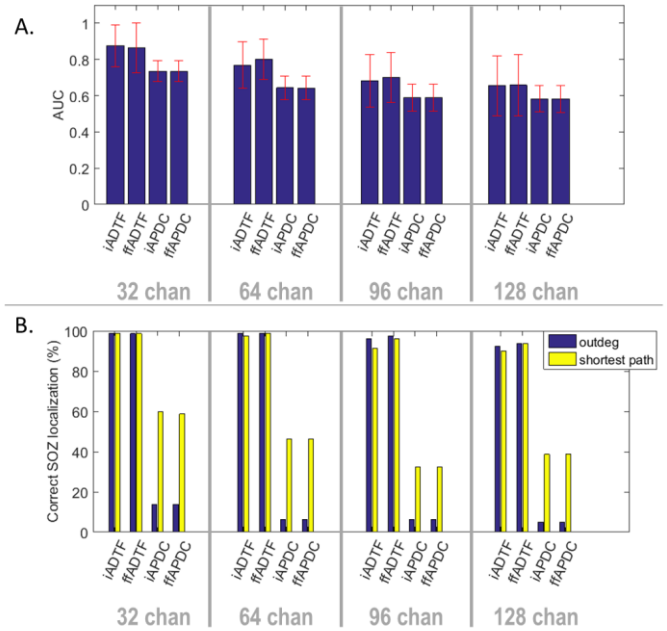

Fig. 3. The results of the simulations. Panel A shows the area under the curve for the different connectivity measures over the different number of channels. Panel B shows the percentage correctly identified seizure onset zones base on graph measures derived from the connectivity measures over the number of channels.

B. Patient data

In table 2 the SOZ localization results using the ADTF and APDC measures coupled to the out-degree and shortest path are shown. The ADTF measures show the same results regardless the graph measures or the number of channels, namely IFG27. This electrode lies in the resection and corresponds with the visual analysis of the epileptologist (OL). For the APDC we see the same results for the out-degree and the shortest path. However, different results are found for the different subsets of included channels. When all channels are included the SOZ localization based on APDC does not correspond with the resection and with the visual analysis of the epileptologist. In Fig. 4 the shortest path and out-degree value of the IFG grid are shown. For the ADTF we find consistent results over graph measures and number of channels included, while for the APDC the results are not consistent.

TABLE II. SOZ LOCALIZATION IN THE PATIENT

	#chan	iADTF	ffADTF	iAPDC	ffAPDC
Out-degree	25	IFG27	IFG27	IFG26	IFG26
	64	IFG27	IFG27	IFG37	IFG37
	113	IFG27	IFG27	SF6	SF6
Shortest path	25	IFG27	IFG27	IFG26	IFG36
	64	IFG27	IFG27	IFG37	IFG37
	113	IFG27	IFG27	SF6	SF6

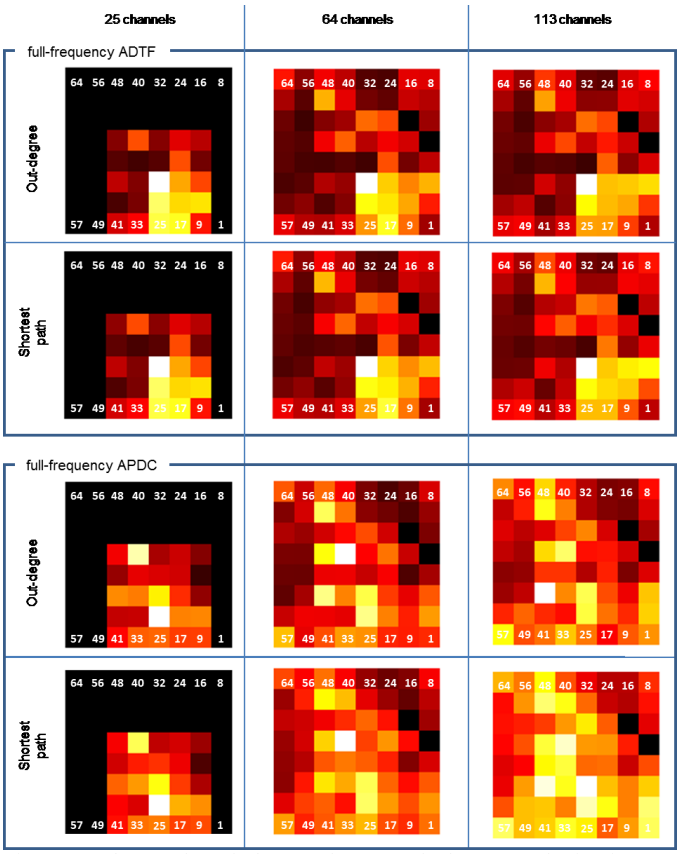

Fig. 4. The results of the out-degree and shortest path for iADTF, ffADTF, iAPDC and ffAPDC for the IFG electrodes. The color corresponds with SOZ localization. The whither the more likely to be the SOZ. The white numbers indicate the IFG electrodes.

IV. Discussion

A. Simulations

The seizure model used in the simulations is a simple model in which time series are delayed to mimic directed functional connectivity between the signals. Despite the fact that in real life the coupling between groups of neurons is more complex, these simple simulations already provide a good insight in how the different connectivity measures perform, which graph measures should be used and what the influence is of the number of channels used in the SOZ localization analysis.

We chose to use sensitivity and precision to calculate the AUC and not the commonly used sensitivity and specificity because the number of TN is very high in the simulations. This means that the specificity = TN/(TN+FP) will always be close to 1 when TN >> FP. In this case the precision = TP/(TP+FP) is a better evaluation measure to investigate the influence of the FP in the simulations.

The ADTF outperforms the APDC to localize the SOZ. This is expected because the ADTF models cascade (indirect) flows, while the APDC models the direct flows. This means that the out-degree of the ADTF can be seen as a global outgoing flow including cascade flow, while for the APDC the out-degree only reflects the local out-going connections. An example of this is represented in fig.1, where there are 31 outgoing cascade connections from node 91, while there are only 3 local outgoing connections. The shortest path works better for the APDC than the out-degree, because the shortest path includes indirect paths over other nodes. The APDC, however, is a useful measure when one wants to investigate the individual directed connections in the network.

Based on the AUC, the ADTF is more sensitive than the APDC to the increase in the number of channels, while the opposite is noticed for the percentage of correctly localized SOZ. This means that the individual ADTF connections are more affected than those of the APDC when channels are added to the analysis. Despite this, the ADTF network remains more valuable than that of the APDC to localize the SOZ.

B. Patient data

The ADTF results were consistent over the number of included channels and pointed to an electrode in the resection. For the APDC results were more variable over the number of included channels and did not correspond to the resection when all channels were included in the analysis. This corresponds with the simulations where the ADTF was also the preferred measure to localize the SOZ.Limitations and future work

Only one seizure of one patient who had a relatively large resection in which many electrodes were situated was analyzed. More patients are needed to show the true value of SOZ localization using functional connectivity from many iEEG channels. Especially patients with more focal visually identified SOZ and smaller resection beds need to be investigated.

The benefit of localizing the SOZ more focally compared to visual analysis is that it could lead to a more tailored/smaller resection and more focal neurostimulation. However, prospective studies that perform resections or neurostimulation based on connectivity results need to be done to investigate the true added value of more focal localization compared to visual analysis.

The designed framework can also be applied to estimate connectivity between sources in the brain after EEG source imaging (ESI). Studies have showed the potential of combining ESI with directed functional connectivity to localize the SOZ [12] and to investigate differences between left and right temporal lobe epilepsy [13]. With the increased use of high density scalp EEG in clinical practice, the analysis to non-invasively map functional brain networks is gaining interest in the neuroscience community. However, thorough validation of these non-invasive methods using simultaneous intracranial and high density scalp EEG recordings should be performed. Furthermore, thorough validation in a large patient group is necessary before the techniques can be used in clinical practice and have an impact on patient management.

ACKNOWLEDGMENT

This project has received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Sklodowska-Curie grant agreement No 660230.

REFERENCES

[1] MA. Kramer and SS. Cash, "Epilepsy as a disorder of cortical network organization," Neuroscientist., vol. 18, no. 4, pp. 360-72, 2012.

[2] F. Rosenow and H. Luders, "Presurgical evaluation of epilepsy," Brain, vol. 124, no. 9, pp. 1683–1700, September 2001.

[3] E. Carrette, K. Vonck, V. De Herdt, A. Van Dycke, R. El Tahry, A. Meurs, R. Raedt, L. Goossens, M. Van Zandijcke, G. Van Maele, V. Thadani, W. Wadman, D. Van Roost, and P. Boon, "Predictive factors for outcome of invasive video-EEG monitoring and subsequent resective surgery in patients with refractory epilepsy," Clin Neurol Neurosurg., vol. 112, no. 2, pp. 118-26, February 2010.

[4] P. van Mierlo, M. Papadopoulou, E. Carrette, P. Boon, S. Vandenberghe, K. Vonck, and D. Marinazzo, "Functional brain connectivity from EEG in epilepsy: seizure prediction and epileptogenic focus localization," Prog Neurobiol., vol. 121, pp. 19-35, October 2014.

[5] KJ. Friston, CD. Frith, PF. Liddle, and RS. Frackowiak, "Functional connectivity: the principal-component analysis of large (PET) data sets," Journal of cerebral blood flow and metabolism, vol. 13, no. 1, pp. 5–14, 1993.

[6] P. van Mierlo, E. Carrette, H. Hallez, R. Raedt, A. Meurs, S. Vandenberghe, D. Van Roost, P. Boon, S. Staelens, and K Vonck, "Ictal-onset localization through connectivity analysis of intracranial EEG signals in patients with refractory epilepsy," Epilepsia, vol. 54, no. 8, pp.1409-18, August 2013.

[7] C. Wilke, W. van Drongelen, M. Kohrman, and Bin He, "Neocortical seizure foci localization by means of a directed transfer function method," Epilepsia, vol. 51, no. 4, pp. 564–72, April 2010.

[8] OA. Petroff, DD. Spencer, II. Goncharova, and HP. Zaveri, "A comparison of the power spectral density of scalp EEG and subjacent electrocorticograms," Clin Neurophysiol., vol. 127, no. 2, pp. 1108-12, February 2016.

[9] I. Blümcke, M. Thom, E Aronica et al., "The clinicopathologic spectrum of focal cortical dysplasias: a consensus classification proposed by an ad hoc Task Force of the ILAE Diagnostic Methods Commission," Epilepsia, vol. 52, no. 1, pp. 158-74, 2011.

[10] CWJ. Granger, "Investigating Causal Relations by Econometric Models and Cross-spectral Methods," Econometrica, vol. 37, no. 3, pp. 424-438, 1969.

[11] P. van Mierlo, E. Carrette, H. Hallez, K. Vonck, D. Van Roost, P. Boon, and S. Staelens, "Accurate epileptogenic focus localization through time-variant functional connectivity analysis of intracranial electroencephalographic signals," Neuroimage, vol. 56, no. 3, pp.1122-33, June 2011.

[12] A. Coito, M. Genetti, F. Pittau, GR. Iannotti, A. Thomschewski, Y. Höller, E. Trinka, R. Wiest, M. Seeck, CM. Michel, G. Plomp, and S. Vulliemoz, "Altered directed functional connectivity in temporal lobe epilepsy in the absence of interictal spikes: A high density EEG study," Epilepsia, Feb 2016, in press.

[13] L. Ding, GA. Worrell, TD. Lagerlund, and B. He, "Ictal source analysis: localization and imaging of causal interactions in humans," Neuroimage, vol. 34, no. 2, pp.575-86, January 2007.