Comparison Between Different Source Localization and Connectivity Metrics of Spiky and Oscillatory MEG Activities

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Ichrak ELBehy*
University of Sfax,
Faculty of Electronics and Telecommunications,
Department of STIC
Digital Research Center of Sfax, CRNS, Tunisia
ichrakchouda@gmail.com

Abir Hadriche
REsearch Groups in Intelligent Machines, Regim Lab,
Enis, Sfax University
High institute of Music, Sfax, Sfax University
Digital Research Center of Sfax, CRNS, Tunisia
Abir.hadriche.tn@ieee.org

*Corresponding author

Rahma Maalej
University of Sfax,
Faculty of Electronics and Telecommunications,
Department of STIC
Tunis km 10, Cité el Ons, Sfax Technopole,
Sakiet Ezzit, Tunisia
rahmamaalej1234@gmail.com

Nawel Jmail
Miracl Lab, Sfax University
Higher Bisness School, Sfax University
Digital Research Center of Sfax, CRNS, Tunisia
naweljmail@yahoo.fr

Abstract *– Epilepsy is considered the second neurological disease in a coma after stroke. Famous markers of epilepsy are repetitive seizures, their origin is stroma and cortical deformation. A neurologist would be assisted by identifying Epileptogenic Zones EZ when diagnosing epilepsy.. Source localization is utilized to identify regions known as EZ, which are of excessive discharges. It consists of both forward and inverse problems. The forward problem models the head through analytical and numerical methods. The inverse problem can be resolved using several techniques to locate the cerebral abnormal sources, via the electrophysiological recording biomarkers. In our study, we will investigate four distributed inverse problem methods: minimum norm estimation MNE, standardized low-resolution brain electromagnetic tomography sLORETA, maximum entropy on the mean MEM, Dynamic statistical parametric maps dSPM, to define epileptic networks connectivity of spiky and oscillatory events. We will examine the epileptic network connectivity using Phase Locking Value (PLV), Phase Transfert Entropy (PTE) for oscillatory events, cross-correlation (CC), and Granger Causality (GC) for spiky events applied on 5 pharmaco resistant subjects. We suggest rating the effectiveness of these networks in locating EZ through a phase of confrontation within iEEG transitory and oscillatory networks connectivity by exploring concordant nodes, their distance, propagation delays connection strength, and their cooperation in recognition of seizure onset zone. All studied techniques of the inverse problem, connection metrics, for both biomarkers of the 5 patients succeed in detecting at least one part of SOZ. sLORETA provides the highest concordant nodes and the closed one for spiky events using CC and GC. sLORETA also depicts the lowest propagation delay for oscillatory events using PTE. Through the 5 patients, MEM, dSPM, and MNE using CC, CG for spiky events, and PTE, PLV for oscillatory activities provide about 72 % of concordant nodes between MEG and iEEG.*

Keywords*: MEG, Connectivity, Epilepsy, Spike, Oscillation*

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1. INTRODUCTION

Neurologic illness diagnosis is increasingly focusing on noninvasive modalities such as electroencephalography (EEG) and magnetoencephalography (MEG) approaches [1, 2]. EEG and MEG recordings provide a high temporal and spatial precision in highlighting brain activity and malfunction, particularly in epilepsy diagnosis. MEG requires less knowledge regarding cerebral tissue to distinguish the origins of epileptic seizures. This could be a major cause to predispose the benefits of MEG on EEG [3, 4]. As a result, despite its cost, neurologists and biomedical researchers are exploring MEG as a supplementary method for epilepsy diagnosis. Alternatively, numerous brain regions might be involved, either as propagation zones or as epileptic discharge generators [5-7]. To identify accurate EZ, neurologists depend on network connections of MEG characteristic signals [8, 9].

Examining and assessing the network connection of MEG biomarkers (spikes and oscillatory events) [10-12] is required, beginning with source localization (forward and inverse issue) [13-15] and progressing to calculating connectivity measures [16]. Four distributed inverse methods are proposed to be investigated: minimum norm estimation MNE [17], dynamic statistical parametric maps dSPM [18], standardized low-resolution brain electromagnetic tomography sLORETA [19], and Maximum Entropy on the Mean MEM. To compare connectivity measures of epileptic spiky and gamma oscillatory events, two connectivity metrics of each event are used. Functional connectivity can be computed using several approaches, like phase synchronization measures [14], amplitude envelope correlation [20], information theoretical approach [21], and other methods.

In this study, the effectiveness of the inverse problem approaches is evaluated by exploring different connectivity metrics of two types of biomarkers to define seizure on set zones and epileptic network complexity. These inverse approaches (MNE, dsPM, sLoreta, MEM) are distributed methods that use the same initial assumptions to construct active zones with alternative hypotheses. MNE normalizes the current density map and Minimum norm estimation (MNE). It has the advantage of not requiring a specific number of sources in advance. Whereas dsPM uses noise covariance for normalization, and substitutes noise covariance with data covariance. sLORETA supposes that the entire brain areas are active within smoother maps. Finally, MEM is a technique for locating dispersed sources originally proposed that cortical parcels would be used to organize brain activity, with each active parcel. Hence, MEM can estimate a contrast of current density within each active parcel.

Connectivity brain measures are intended to look at how cortical networks interact with each other. There are three types of connection between regions: structural ("directed functional connectivity"), functional ("non-directed statistical associations"), and effective ("causal interactions"). Using Brainstorm, multiple connection measures are computed for directed and non-directed functional connectivity investigations.

Functional connectivity is estimated using Phase Locking Value (PLV) which is an alternative class of measures that considers only the relative phase of two signals by computing a phase locking value between them [22, 23]. The concept of phase locking is fundamental in dynamical systems and has been used in control systems (the phase-locked loop) as well as in the analysis of nonlinear, chaotic, and non-stationary systems. Since the brain is a nonlinear dynamical system, phase locking is a suitable method for quantifying the interaction of oscillatory gamma events. Phase Transfer Entropy (PTE) is an instantaneous phase time series, quantified by phase transfer entropy (PTE) [24]. PTE estimates whether the past of both source and target time series influences the ability to predict the target time series' future which is also suited for studying gamma networks. Correlation is a non-directed connectivity metric that measures the relationship of two time series. Without further preprocessing of the input time series. Correlation is sensitive to volume conduction and is not frequency specific chosen to determine spiky networks. Finally, GC is a functional connectivity [25], developed in economics but recently piqued the interest of the neuroscience community since it enabled statistical influence to be estimated without the need for direct intervention [26] and also chosen to compute spiky networks.

This preprocessing chain was applied on 5 pharmaco-resistant epileptic subjects, where neurologists examined and proved the efficacy of studied biomarkers (spiky and gamma oscillatory events).

As a result, MEG concordant nodes were determined, and connection strength propagation delays and their cooperation in recognition of seizure onset zone SOZ were computed. Through 5 patients, sLORETA exhibits the highest concordant nodes and the lowest propagation delays, for both biomarkers. All proposed inverse problems within connectivity measures provide at least one part of SOZ and about 72% of nodes are detected by MEG and seen in iEEG. CG and PTE enhance the connection strength for spiky events and oscillatory activities respectively.

2. MATERIALS AND METHODS

2.1. MATERIALS

EEGLAB and Brainstorm Toolbox (a freely available collaborative tool for cerebral signal processing) was used for all analysis phases on "MATLAB" Mathwork, Natick, MA [27].

The explored signals were both MEG and iEEG for five pharmacoresistant subjects [28]. This research involved a magnetoencephalography MEG registration for 5 patients with drug-resistance epilepsy. Acquisition and preprocessing steps were used in the clinical Neurophysiology Department of Marseille's "La Timone" hospital. An experienced neurologist (M.G.) validated patients with constant and frequent epileptic spiky and gamma activity. Registration was made with closed eyes and no activation method or movement, a 151-gradiometer device (CTF Systems Inc., Port Coquitlam, Canada) was used to capture the MEG signal. 20 epochs of 5 s each of sampling at 1025 Hz were recorded.

Intracerebral EEG signals were gathered as the Talairach stereoscopic method [22], sampled at 512Hz. Clinical, neurophysiological, and anatomical features of each patient as in [5] were taken into consideration to designate cerebral marks. CT scan and MRI examinations were detailed in [5].

In this study, for each subject, an average of 30 epileptic spikes and gamma oscillations were investigated. In total, about 300 spiky events and oscillatory ones were studied [5].

Additionally, the Institutional Review Committee of the French Institution of Health INSERM gave its approval to our experiment. The clinical data for our patients is shown in Table 1 [5].

Table 1. The clinical data for our patients

Patients	Gender/ age	Structural MRI	Histological diagnosis	MEG spike occurrence	MEG: preop versus post-op	Epilepsy surgery	Surgical outcome. Engel class (follow up)
1-BeA	F17	R lateral occipitotemporal FCD	FCD	Subcontinuous	Preoperative	R occipitotemporal cortectomy	Class 3 (8 years)
2-ZC	F26	Normal	Gliosis	Abundant	Preoperative	L occipitotemporal cortectomy	Class 3 (5 years)
3-BC	F25	L premotor FCD	FCD	Abundant	Preoperative	L premotor cortectomy	Class 3 (6 years)
4-DT	M25	R basal occipitotemporal FCD	FCD	Abundant	Preoperative	R anterior temporal lobectomy	Class 2 (2 years)
5-BoA	F31	R parietal ischemia	Gliosis	Abundant	postoperative	R parietal cortectomy	Class 4 (7 years)

2.2. METHODS

Brainstorm, EEGlab [27], Fieldtrip toolbox, and MATLAB (MathWorks, Inc.) tools were used for all signal preprocessing.

As in [5], spiky and oscillatory events were selected visually by an expert, and then a filtering step was applied to eliminate artifacts and overlap between activities. Time windows of joined spikes and oscillations independently are made. FIR filtering is applied on each window: a band-pass filter [10 45] Hz was used to eliminate slow component of spiky windows and [29] Hz for oscillatory windows. For both filters, the ripple amplitude is equal to Rp = 3 %, and the attenuation in the stop band is Rs = 30 dB.

2.2.1. Source Localization of MEG Signal

Forward Problem is a way to describe the head using analytical and numerical approaches such as boundary element method (BEM), finite element method (FEM), and finite difference method (FDM). Since the thickness of our skull is not uniform across the head, MRI determines local conductivity characteristics. Furthermore, the forward problem is solved as described in [13], by creating a multiple spheres head model for each patient. BrainVisa software was used to segment and mesh the cortex and scalp surfaces. Finally, Matlab's Brainstorm toolbox is used to register the MRI and sensors of each analyzed patient [5-24].

Inverse problem is explored to define sources that generate scalp measurements (MEG in our case) to understand cerebral function and dysfunction [30, 13, 14]. For epilepsy, the inverse problem of source localization is solved to recognize relative regions of excessive discharges and seizure buildup (damaged cerebral tissue [31]. An inverse problem is an underdetermined problem (multiple sources can yield the same potential field) so there is no unique solution. Therefore, to identify an effective solution, different hypotheses (neurophysiological, biophysical, and anatomical) as well as regularization approaches are tested and applied. Dipolar source localization was investigated as a solution, however assumption about employed dipole number leads researchers to adopt scattered approaches.

The four proposed inverse problem methods are based on a 3D current source solution grid with fixed positions configuration that necessitates only regularization parameters to reduce the noise effect and ensure a stable source configuration. These techniques didn't require a prior source number constraint as the dipolar solution did. They provide different aspects of source localization: from simplicity and computational efficiency of MNE to statistical robustness of dSPM, precision localization capabilities of sLORETA, and incorporation of prior information in MEM. Moreover, these methods are suitable for analyzing both spiky and oscillatory events, which are crucial for understanding the dynamics of epileptic seizures" [32].

In the next section, the explored four distributed inverse problem approaches: MNE, dSPM, sLORETA, and MEM are briefly described.

Minimum norm estimation (MNE)

Minimum norm estimation (MNE) has the advantage of not requiring a specific number of sources in advance. On the other hand, it necessitates a regularization that may affect on chronological series estimation: cross-talk between sources. As a result, imposing a parsimony constraint on sources may be beneficial. An original solution of 3D current configuration that matches the analyzed signal within a minimum intensity (smallest L2-norm) is offered by the minimum norm estimate (MNE) described by [33]. MNE was proposed by [33]. It achieved an exceptional 3D current configuration solution that fits the signal under within the lowest intensity (smallest L2- 277 norm). This hypothesis can drown deeper sources since MNE focuses on superficial sources. The MNE formula is shown in Equation 1.

$$SS_{MNE} = G^T(GG^T + \lambda C)^{-1}G \quad (1)$$

λ Indicates the regularization parameter, while C represents the noise covariance matrix.Weighted solutions of MNE may be found in dSPM, eLORETA, and cMEM (their formula is based on MNE sources, S_MNE).

Dynamical Statistical Parametric Mapping (dSPM)

Dale et al. Suggest Dynamical Statistical Parametric Mapping (dSPM) as a different inverse problem solution. Dale et al. recommend a normalization based on a minimum norm estimate of each source noise (obtained from the MNE noise covariance matrix) as an inspiration from MNE [34-36].

Equation 2 describes dSPM as a least-squares or weighted minimal norm solution.

$$S_{dsPM} = W_{dsPM} S_{MNE} \quad (2)$$

$$W^2_{dsPM} = diag(S_{MNE} C S^T_{MNE}) \quad (3)$$

Standardized LOw Resolution brain electromagnetic tomography (sLORETA)

According to Pascual-Marqui RD [29], the entire brain regions are activated in sLORETA's smoother maps. sLORETA swaps the noise covariance with data covariance, which accounts for uncertain number of simultaneous source activations. The ratio of the covariance matrix of sources to the gain matrix is the inverse operator L for the sLORETA technique.

$$L = R/J \quad (4)$$

R represents the source covariance matrix, assumed to be the identity gains matrix.

Maximum Entropy on the Mean (MEM)

MEM is based on a probabilistic (Bayesian) technique to estimate current source intensities from the data's informative content. MEM explores cortical parcels to organize brain activity, with each parcel being active or inactive. MEM estimates the contrast of current density inside each active parcel. The MEM's primary premise is that brain activity is segmented into discrete units. As a result, a source's activity inside a patch is correlated with its neighboring sources. An essential notion that allows MEM to be sensitive to the geographic extent of sources on cortical surfaces is using a spatial model in the MEM framework [37]. Recently, MEM has been expanded to temporal frequency to locate oscillatory and synchronous generators.

2.2.2. Functional connectivity metrics

Measures of brain connectivity enable to define interaction of cortical network. There are three types of connection between regions: structural ("directed functional connectivity"), functional ("non-directed statistical associations"), and effective ("causal interactions").

Multiple connection measures (for directed and non-directed functional connectivity investigations) were determined using Brainstorm. Computing a bivariate measure between two interested geographic time series pairs is a standard method of performing connectivity analysis.

Each brain region can be seen as a node on a connectivity graph representing resulting the connectome, with connectivity metrics displayed above each graph edge. Functional connectivity was estimated using Phase Locking Value (PLV), Phase Transfer Entropy (PTE) for oscillatory gamma activities, and Correlation and Granger causality for spiky events. This choice was justified by the importance and the effect of the frequency factor and the directionality (directed versus non directed). In Table 2, a summary of these functional connectivity metrics was gathered.

Table 2. Functional connectivity metrics

Metrics	Domain	Directionality	Static(s) Dynamic(s)
Correlation	Time	Non directed	S
Granger Causality	Time	Directed	S
Phase Locking Value (PLV)	Phase	Non directed	S
Phase Transfer Entropy(PTE)	Phase	Directed	D

Phase Locking Value (PLV)

An alternative class of measures considers only the relative phase of two signals by computing a phase locking value between them [38, 22]. The concept of phase locking is fundamental in dynamical systems and has been used in control systems (the phase-locked loop) as well as in the analysis of nonlinear, chaotic, and non-stationary systems. Since our brain is a nonlinear dynamical system, phase locking is a suitable method for quantifying cortical interactions.

A more pragmatic reason for using PLV in studies of LFPs, EEG, and MEG is its resistance to amplitude fluctuations (which may contain less information about interactions) [39, 40]. PLV is an absolute value of the mean phase difference between two signals expressed as a complex unit-length vector [37-40]. If marginal distributions of two signals are uniform and signals are independent, the relative phase will be uniform and equal to zero, otherwise, (for strongly coupled signals), PLV approaches unity. PLV is frequently used to describe phase synchronization between two narrow-band signals. Consider a pair of real signals, $S_{1(t)}$ and $S_{2(t)}$, which have been band-pass filtered to a desired frequency range. The Hilbert transform can be used to obtain analytical signals from $S_{1(t)}$ and $S_{2(t)}$:

$$z_{i(t)} = s_{i(t)} + \mathrm{HT}\,(s_{i(t)}) \quad (5)$$

Using analytical signals, relative phase between $z_{1(t)}$ and $z_{2(t)}$ can be computed as,

$$\Delta\emptyset(t) = \arg\left(\frac{z_1(t)\, z_2^*(t)}{|z_1(t)||z_2(t)|}\right) \quad (6)$$

The instantaneous PLV is $\mathrm{PLV}(t) = \left|E\left|e^{j\Delta\emptyset(t)}\right|\right|$.

Phase Transfer Entropy (PTE)

PTE is a directed connectivity measure that evaluates transfer entropy (TE) between two instantaneous

phase time series [24]. TE calculates whether the history of both the source and target time series can affect the ability to forecast the target time series' future.

In PTE, if a phase signal $\emptyset\tilde{x}(t)$ causes the signal $\emptyset\tilde{y}(t)$, the mutual information between $\emptyset\tilde{y}(t)$ and the past of $\emptyset\tilde{x}(t)$ is computed.

Cross- Correlation (CC)

Correlation is a non-directed connectivity metric that measures the relationship of two time series, without further preprocessing of input time series. Correlation is sensitive to volume conduction and has no frequency specification. CC of signals gathered from active regions (showing a local energy peak) consists of estimating the degree of similarity between these locations using the correlation coefficient r presented in equation 6.

$$r(\tau) = cov(s1(t), s2(t-\tau))\sqrt{var(s1).var(s2)} \quad (7)$$

Where r is the correlation coefficient derived between two signals (two cortical areas), cov is the covariance, var is the variance, and τ is the offset considered between studied signals.

Granger causality (GC)

Granger causality (GC) is a technique of functional connectivity created by Clive Granger in the 1960s [25] and improved by John Geweke into its current form [41]. GC specializes in economics, but has lately attracted the interest of the neuroscience community.

Previously, neuroscience depended on lesions and stimuli applied to the nervous system portion to investigate their influence on others. However, GC offered statistical measures without requiring direct intervention [26]. Even though GC has been extended to nonlinear, multivariate, and time-varying conditions.

In the time domain, this may be shown as follows: if X represents a signal, it may be represented using a linear autoregressive model estimate (AR model) in two ways:

$$X(\mathrm{t}) = \sum_{k=1}^{p}[A_k x(t-k)] + e_1 \quad (7)$$

$$X(\mathrm{t}) = \sum_{k=1}^{p}[A_k x(t-k) + B_k y(t-k)] + e_2 \quad (8)$$

p is the quantity of previous knowledge that will be used to forecast future samples, also known as model order. In both expressions, the first model X uses only its history (and present), but the second includes the past (and present) of a second signal y. The model considers just past signals ($k \geq 1$) and ignores the current connection, making it less vulnerable to volume conditions.

The measure of GC is defined as follows:

$$F_{y\to x} = \ln\left(\frac{var(e_1)}{var(e_2)}\right) \quad (9)$$

0 if $var(e_1)$=$var(2)$ and a non negative $if^{var}(e_1) > var(2)$.

$var(e_1) \geq var(2)$ Always holds, as the model can only improve when adding new.

3. RESULTS

In Fig. 1, active areas of selected epileptic spiky MEG data using MNE, dSPM, sLORETA, and MEM are depicted. MNE, dSPM, and sLORETA methods produced numerous active regions ROI (Region Of Interest), while MEM produced noticeably fewer active regions.

The four distributed inverse problem methods are explored to evaluate the coupling rate between active regions of the subject using 20 scouts in each hemisphere. For each Region of Interest (ROI), time series for both spiky and gamma oscillatory activities have been reconstructed.

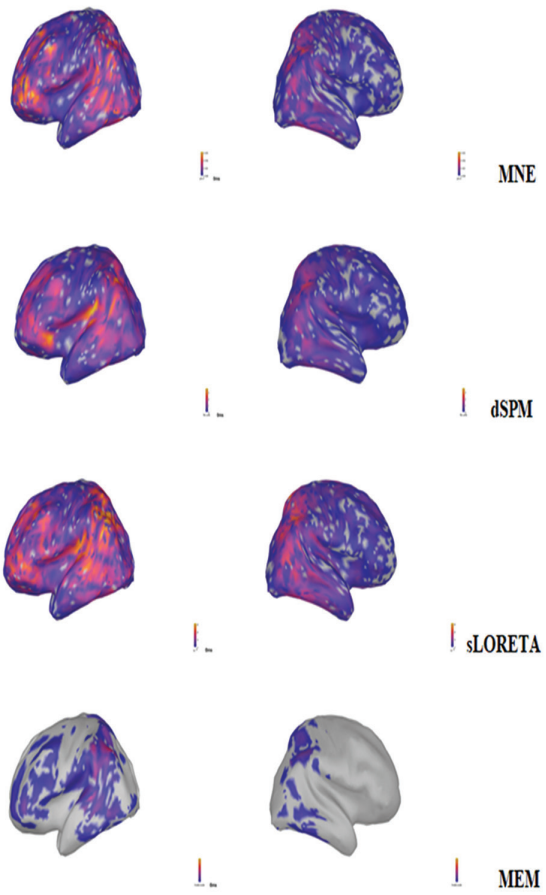

Fig.1. Active regions using 4 inverse problem methods (MNE,dSPM,sLORETA, and MEM) of spiky events

The proposed connectivity metrics are computed: Phase Transfer Entropy (PTE), Phase Locking Value (PLV) for oscillatory events, cross- correlation (CC), and Granger Causality (GC) for spiky events, as non-directed and directed functional connectivity analyses using Brainstorm.

Connectivity scores are shown as links drawn between regions of interest. These ROI are displayed as nodes labeled along graph circumference with Intensity threshold, (minimum or maximum connectivity.

In Fig. 2, GC is presented as a timing directed static measure of patient 1 spiky connectivity networks obtained by MNE, sLORETA, MEM, and dSPM.

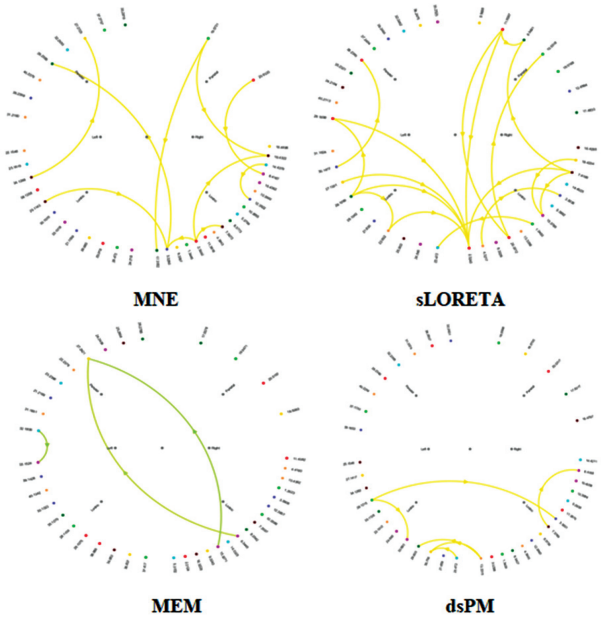

Fig. 2. Epileptic spiky network connectivity for patient 1 using Granger Causality obtained by:MNE, sLORETA, MEM, and dsPM

For the following figure, lags are imposed in the range [-149, 150] ms, the maximum threshold in each method is set to 2.00, and distance filtering to 0 mm. Connectivity is depicted by a link with direction "in" or "out" thanks to this metric specification, a measure of directed functional connectivity is obtained. dsPM shows a strong connection between ROI and MEM represents a weak connection.

Fig. 3 depicts the gamma oscillatory connectivity networks of patient 1 obtained by MNE, sLORETA, MEM, and dsPM using PLV as a phase non directed, static connectivity metric.

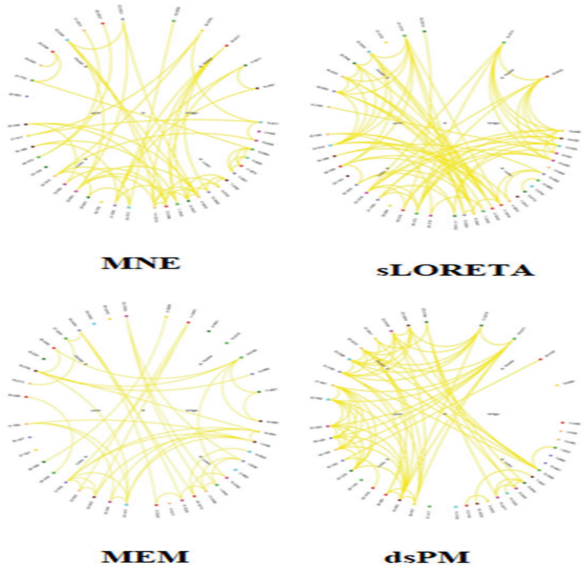

Fig. 3. Patient 1 gamma network connectivity obtained by: MNE, sLORETA, MEM, and dsPM using PLV

In Figure 3 lags in the range [-149, 150] ms are imposed. The maximum threshold in each method was set to 0.99 and distance filtering to 0 mm. A frequency band between 15 and 45 Hz (that admits the gamma band) was chosen. MNE shows a strong connection between ROI and dsPM represents a weak connection.

In Figure 4, we gathered nodes in common and a number of links between active regions for patient 1 spiky events using 4 inverse problem techniques and two metrics (CC and GC) for each one.

For both CC and GC, MEM depicts the lowest number of connections and nodes in common, hence MEM presents the lowest complexity for epileptic spiky networks.

In Fig. 5, nodes in common and several links between active regions for patient 1 gamma oscillatory events using 4 inverse problem techniques and two metrics (PLV and PTE) for each one are depicted.

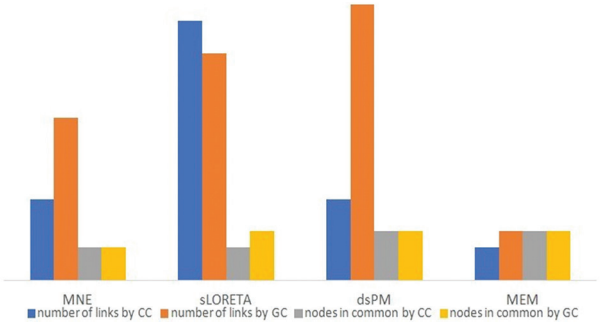

Fig.4. Patient 1 nodes in common and several links for spiky events using 4 inverse problem techniques and two metrics (CC and GC)

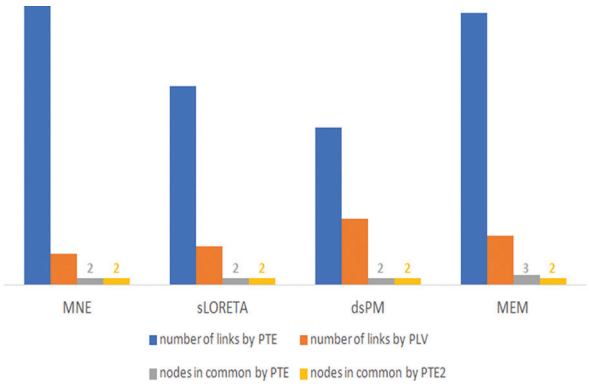

Fig. 5. Patient 1 nodes in common and several links for gamma events using 4 inverse problem techniques and two metrics (CC and GC)

For both PLV and PTE, MEM depicts the lowest number of connections and nodes in common, hence the lowest complexity of epileptic oscillatory networks. Nevertheless, MEM was able to detect parts of SOZ.

The connectivity strength of each metric of studied methods is computed, in which maximum, mean, and minimum values are applied, and depicted in Fig. 6.

GC as a functional connectivity metric provides high-

er connection strength for entire investigated inverse problem techniques with a slightly important value for sLORETA

In Fig. 7, the maximum, median and, minimum distance between common MEG nodes for the distributed methods applied to epileptic oscillatory events of patient 1 are depicted.

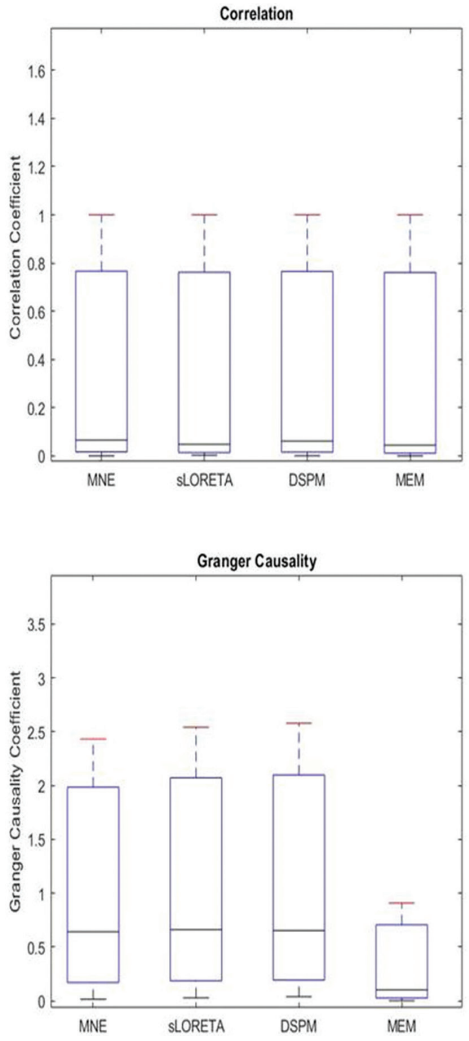

Fig. 6. Connection strength, by: MNE, sLORETA, MEM and, dsPM using CC, and GC for epileptic spiky events

For both connectivity measures, MNE depicts the closest nodes of interest within an average distance of 0.6 mm.

In Table 3, the study conducted on spiky and gamma events (using 4 distributed inverse problem techniques and 2 connectivity metrics) applied on patients in recognition of SOZ and propagation delays is gathered.

For the entire sets of patients that were investigated in this work, we noticed that the obtained network connectivity for both biomarkers and different inverse problems and metrics provide the same highlighted results (detection of SOZ, nodes in common between depth and surface , propagation delays and distance), within slight differences for patient 4.

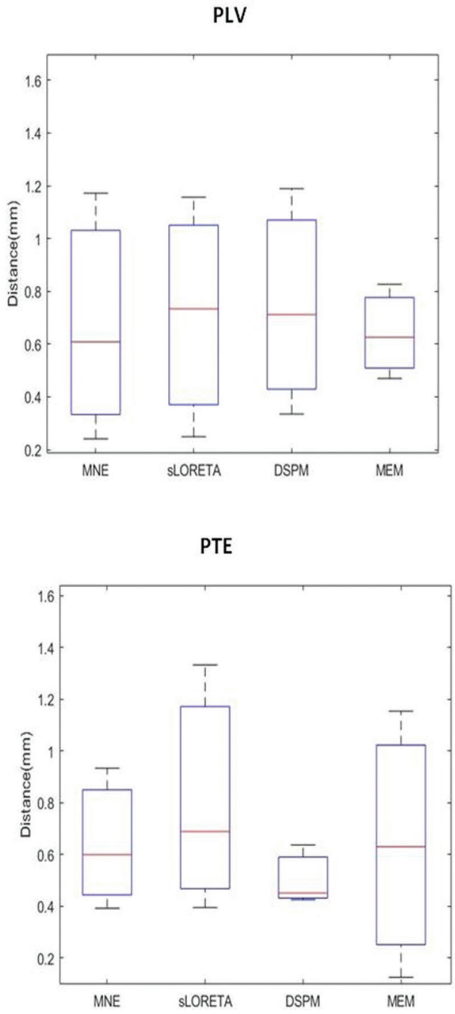

Fig. 7. Maximum, median, and minimum distance between nodes of interest obtained for gamma oscillations networks by PTE and PLV

Table 3. Recognition of SOZ per patient and Propagation delays

Methods	Spiky events		Oscillatory events	
	SOZ recognition	Average propagation Delays in ms	SOZ recognition	Average propagation Delays in ms
Non-directed MNE	yes	22	yes	24
directed MNE	yes	21	No	23
Non-directed sLORETA	yes	18	yes	20
directed sLORETA	yes	19	yes	19
Non-directed dSPM	yes	22	yes	23
directed dSPM	yes	22	yes	24
Non-directed MEM	No	24	yes	25
directed MEM	yes	23	no	23

4. DISSCUSION AND CONCLUSION

In this study, the relationship between epileptic spiky, and oscillatory events for 5 pharmaco-resistant patients [5] was established. Rating the effectiveness of a given inverse problem combining two connectivity metrics (directed and non-directed one) in locating epileptic zones was suggested. To explain cortical regions and neuronal generators of excessive discharges , we first applied four inverse problem approaches: MNE, sLORETA, dSPM, and MEM. Each technique's network connectivity using two types of connectivity metrics was computed. We investigated CC and GC for spiky activity to explore the causality effects on epileptic spiky events. Then, PLV & PTE for gamma oscillatory events were proposed to evaluate the phase synchronization effects on epileptic oscillatory networks. For both biomarker sLORETA depicts the highest number of nodes in common for directed and non directed functional connectivity; also it presents the closet nodes and the lowest delay propagation. The entire investigated inverse problem techniques and for directed and non directed functional connectivity were able to recognize parts of SOZ. CG enhances the strength of connectivity for spiky networks and PTE for oscillatory events.

This proves the effect of causality on networks' spiky topology. In this work, the distributed inverse techniques depict different topologies of networks. However, their results concerning nodes in the common delay of propagation and mutual between invasive and non invasive networks are quite close. Also, we noticed that directed and non directed metrics of connectivity did impact the complexity of networks for both biomarkers; but it doesn't change radically the studied networks. The techniques investigated could be considered as a prognosis tool for studying epileptic network connectivity.

In this study, four distributed inverse methods were investigated in the context of defining epileptic network connectivity tested on 2 types of biomarkers. A robust comparative analysis that enhances the robustness of each method in real clinical scenarios was proved. Moreover, advanced connectivity metrics directed and non-directed are explored to test the topology of network connectivity, then confronted with IEEG network connectivity. This dual approach gave a further level of analysis of epileptic network connectivity, addressing a gap in previous research which often focused on a single type of event, method, or metric. Our findings have significant implications for the presurgical evaluation of epilepsy patients, by demonstrating that all studied techniques successfully detect at least one part of the seizure onset zone (SOZ)

Hence to further examine and assess tools for the definition of exact cerebral generators responsible for excessive discharges and build-up of seizure using MEG signal, testing additional sets of patients as a future work is suggested. A second track that could be also interesting is to compare outcomes of other distributed techniques, including ST-MAP (SpatioTemporal-Maximum A Posteriori), MCE (minimum current estimates), and Eloreta (exact low-resolution brain electromagnetic tomography) applied on a combination of several registration techniques.

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