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Stanislas Lagarde, Christian-George Benar, Fabrice Wendling, Fabrice Bartolomei. Interictal functional connectivity in focal refractory epilepsies investigated by intracranial EEG. *Brain connectivity*, 2022, 12 (10), pp.850-869. 10.1089/brain.2021.0190 . hal-03768069

**HAL Id: hal-03768069**

**<https://hal.science/hal-03768069>**

Submitted on 2 Sep 2022

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# Interictal functional connectivity in focal refractory epilepsies investigated by intracranial EEG

Short Running Title: Interictal iEEG connectivity in focal epilepsies

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**Key Words:** partial epilepsy, drug-resistant epilepsy, functional connectivity, EEG, SEEG, epilepsy surgery

## **ABSTRACT**

Focal epilepsies are diseases of neuronal excitability affecting macroscopic networks of cortical and subcortical neural structures. These networks ("epileptogenic networks") can generate pathological electrophysiological activities during seizures but also between seizures (interictal period). Many works attempt to describe these networks by using quantification methods, particularly based on the estimation of statistical relationships between signals produced by brain regions, namely Functional connectivity (FC). FC has been shown to be greatly altered during seizures and in the immediate peri-ictal period. An increasing number of studies have shown that FC is also altered during the interictal period depending on the degree of epileptogenicity of the structures. Furthermore, connectivity values could be correlated with other clinical variables including surgical outcome. This leads to a conceptual change and to consider epileptic areas as both hyperexcitable and abnormally connected. These data open the door to the use of interictal FC as a marker of epileptogenicity and as a complementary tool for predicting the effect of surgery.

In this article, we will review the available data concerning interictal FC estimated from iEEG in focal epilepsies and discuss it in the light of data obtained from other modalities (EEG, MEG, MRI) and modelling studies.

**Impact Statement:** In this article, we review the concepts of epileptogenic network and explained the basic notions of functional connectivity and the potential biases when studying it using intracranial EEG. We report the current body of published data using intracranial EEG. These data demonstrate that even at temporal distance from epileptic seizures there are differential changes in functional connectivity between areas epileptic or not. It appears that the connectivity of epileptic zone remains relatively preserved and higher than the connectivity of none-epileptic zone (decreased). These data could help in locating epileptic areas and predicting surgical outcome.

**List of Abbreviations:**

*EZ: epileptogenic zone; PZ: propagation zone ; NIZ : non-involved zone ; RZ : resection zone ; IZ: irritative zone; iEEG : intracranial EEG ; SEEG: stereo-EEG; ECoG: electrocorticography; FCD: focal cortical dysplasia; CCEP: cortico-cortical evoked potential; h2: non-linear correlation coefficient; DTF: directed transfer function; PDC: partial directed coherence; AUC: area under the curve; DBS: deep brain stimulation, VNS: vagal nerve stimulation; IED: interictal epileptiform discharge; TLE: temporal lobe epilepsy*

# MAIN BODY

## 1. INTRODUCTION

### **Focal refractory epilepsy and the concept of epileptogenic network**

Epilepsy is a serious and highly prevalent neurological disease, affecting more than 1% of the population worldwide (Fiest et al., 2016) and associated with a significant overmortality and frequent comorbidities (Thurman et al., 2017). Approximately 60% of patients with epilepsies have focal seizures (Hauser et al., 1991). Pharmacoresistance to antiseizure medications remains a major issue for up to one-third of patients (Kwan et al., 2000). In these cases, epilepsy resective surgery, when possible, is the best option (Kalaivani et al., 2017; Ryvlin et al., 2014; Wiebe et al., 2001). For these patients with drug-resistant focal epilepsies, the main prognostic factor of surgery is to achieve complete resection of the epileptogenic zone (EZ), the latter being defined on the basis of multimodal data (clinical, EEG, MRI, PET). In some cases, non-invasive data are not sufficient to accurately define the EZ and its relationship with eloquent cortices. In these cases, intracranial EEG (iEEG) recordings are mandatory (Isnard et al., 2017; Jayakar et al., 2016). Such iEEG recordings have led to the observation that focal epilepsy is often organised as a network with regards to the spatial organization of EZ, pattern of seizure propagation, and connectivity alteration induced by recurrent seizures (*for a review see* (Bartolomei et al., 2017)). In the last fifteen years, the notion of “Epileptogenic networks” has become more and more popular in epileptology (Bartolomei *et al.*, 2017) since its first description in the early 2000s (Bartolomei et al., 2001; Spencer, 2002). In this context, the important breaking point is to replace the concept of epileptic focus (Rosenow and Luders, 2001) by that of epileptogenic networks.

This model involves spatio-temporal dynamics in the genesis of ictal and interictal activities between a more or less extended set of distant brain regions. In this model, there is a hierarchy of brain regions ranked according to their epileptogenicity: 1) EZ network, 2) Propagation zone (PZ) network and 3) Non-involved zone (NIZ) network (Figure 1). Indeed, the analysis of iEEG recordings of seizures often reveals an involvement of multiple cerebral structures, sometimes with different types of discharges (more or less rapid) and with variable delays of involvement. It is thus not always easy to define the limits of the area to be resected, especially in the case of short involvement times and extensive rapid discharge at seizure onset. Quantified analyses of seizure onsets actually show a gradient of epileptogenicity between the different structures involved (Bartolomei et al., 2017, 2008). The EZ network concerns the regions involved earlier in the seizure with the most rapid discharges, whereas the PZ network concerns regions involved later or via less rapid discharges. Interestingly, studies with other modalities (PET, MRI) also show such a gradient in the observed alterations (metabolic, structural connectivity respectively)(Besson et al., 2017; Lagarde et al., 2020).

The MRI visible lesion and the areas generating interictal paroxysms could, according to the patient, belong to one or more of the above ictal-defined (Epileptogenic, Propagation, Non-involved) networks. While numerous studies have shown modified brain synchrony during seizures (pre-ictal, ictal, and post-ictal states) (see review in (Bartolomei et al., 2017)), cerebral connectivity is also notably altered during interictal period. However, pre-ictal, ictal and inter-ictal data reflects distinct pathophysiological processes and should not be mixed up when interpreting the existing literature. We will focus the present review on the functional connectivity alterations observed remotely from seizures, i.e. in the interictal period.

## **Functional connectivity**

Functional connectivity refers to the statistical link that can exist between activities recorded from distinct brain structures, reflecting more or less synchronized functioning of underlying neuronal populations. The first methods of functional connectivity analysis from EEG signals were developed in the 1950s (Barlow and Brazier, 1954), and first application to ictal signals in the 1980s (Gotman, 1983). The methods have developed in the following years, particularly with the rise of computers and digital EEG systems. Today, the range of methods that can be used to estimate functional connectivity is wide. These methods have been evaluated in studies using simulated signals (Ansari-Asl et al., 2006; Wang et al., 2014). The conclusion of these studies is that no method is universal (i.e., most efficient in all the situations tested). They show different performance depending on the type of model and the data used (electrophysiology or fMRI). Another observation is a strong influence of the choice of the frequency band of interest (Courstens et al., 2016). Still, methods belonging to the family of linear and non-linear correlations proved to be a good compromise in various tested models (Wang et al., 2014; Wendling et al., 2009).

Functional connectivity at the macroscopic scale can be measured by EEG (scalp or intracranial), MEG and functional MRI. Functional MRI is an indirect marker of neural activity via the hemodynamic response. It should be noted that this hemodynamic response is delayed after the variation in neural activity (e.g. about 5 seconds after the start of a stimulus) (Logothetis, 2008). Thus, if fMRI allows whole brain exploration, derived measures of connectivity can only be estimated over relatively slow timescales (seconds). The data concerning MRI connectivity in focal refractory epilepsies have been reviewed in previous works (Bernhardt et al., 2013; Tavakol et al., 2019) and will not be the topic of this review.

Both MEG and EEG offer high temporal resolution and allow for analysis of neural activity at the millisecond scale. Despite whole brain covering, with some limitations for deep structures, their spatial resolution is limited to the study of regions with a volume of  $1\text{ cm}^3$ . Moreover, it is necessary to solve the inverse problem to go from the sensor to the brain sources level. In this context, volume conduction effect and sources leakage may influence the results of connectivity. However, several methods have been developed, notably source imaging and also specific connectivity analyses (e.g. imaginary part of coherence), to limit this problem (He et al., 2019). It should be noted that this problem of volume conduction is not absent in intracranial EEG either. A review concerning Interictal functional connectivity data in EEG and MEG can be found in (van Mierlo et al., 2019).

Intracranial EEG recordings (iEEG) bring complementary information to EEG/MEG data by higher spatial resolution (with sampling at the  $\text{mm}^3$  level) and excellent temporal resolution, (ms, equivalent to scalp EEG and MEG), yet incomplete brain sampling. Two main techniques of iEEG recording are being used in routine: electrocorticography (ECoG) and stereotactic-EEG (SEEG). Several studies have now confirmed that SEEG has lower morbidity than subdural recordings (Jehi et al., 2021; Katz and Abel, 2019; Mullin et al., 2016; Tandon et al., 2019). SEEG has currently gained worldwide popularity due to its favourable morbidity profile, superior coverage of subcortical structures, ability to perform multilobar or bilateral explorations without the need for craniotomy. It is noteworthy that the assessment of functional connectivity and brain networks is not superimposable when using SEEG or ECoG data (Bernabei et al., 2021). SEEG allows to records the activity of multiple and distant brain regions, which are more likely to reveal large-scale network activities, which probably explains why the development of the concept of epileptogenic networks began with the pioneering work in the field (Bancaud and Talairach, 1992; Bartolomei et al., 1999; Chauvel



et al., 1987). However, the number of SEEG electrodes being obviously limited, the spatial sampling remains incomplete, which requires certain precautions to be taken when analysing and interpreting functional connectivity and network metrics from graph theory (*see below*).

A SEEG electrode records local field potentials (LFP) corresponding to the electrical activity of cooperative activity in neuronal populations. Generally speaking, LFP depend on the geometry of dendrites and on the features of the dipole constituted by sinks and sources at the dendrites and soma of pyramidal cells. It is well admitted that LFP reflects several underlying processes such as synaptic potentials, afterpotentials of somato-dendritic spikes, and voltage-gated membrane oscillations (Wendling and Lopes da Silva, 2018). Regarding space, they reflect the mean activity of a neuronal population between 1 mm<sup>3</sup> and 1 cm<sup>3</sup> depending on the geometrical features of the extracellular electrode (micro- to meso-scale) and on the level of synchrony (Logothetis, 2003). In the specific case of SEEG, the exact dimension of the recorded neuronal population is not accurately known. Still, in the last years, several SEEG studies have brought important knowledge on the alterations in interictal functional connectivity that are observed in focal refractory epilepsy. This review aims at providing a detailed description of these data, highlighting methodological issues that should be considered for data interpretation and discussing the remaining questions to address.

## **2. Overview of methods for measuring FC**

### *Functional connectivity estimation*

It has been hypothesized that the synchronization of neuronal oscillations between cerebral areas may allow transfer of information in the brain. Therefore, several quantitative methods have been developed to assess the statistical relationship between signals, namely the functional connectivity. There is now a plethora of available methods, each with its own advantages and disadvantages. These can be distinguished according to some of their characteristics, which we will briefly detail below. Interested readers could find more detailed review on the subject in (Bastos and Schoffelen, 2016; He et al., 2019).

A first distinction can be made between the methods model-based (e.g. linearity assumed for correlation or granger causality) and model-free (e.g. mutual information, transfer entropy and non-linear correlation being sensitive to both linear and non-linear interactions). The simplest measure for estimating linear interactions is the Pearson correlation coefficient, which measures the linear relationship between two variables. Other forms of non-linear coupling exist such as cross-frequency coupling (where the phase or amplitude of a certain frequency interacts with the phase or amplitude of another frequency), then other metrics sensitive to this non-linear coupling have been developed. For example, as the relationship between signals in epilepsy may be more complex than a simple shift, Pijn et al. have thus proposed to use a non-linear model for the transformation, which consists in a non-parametric analysis aiming at quantifying the correlation of a signal Y on a signal X, independently of the type of the relation between the two signals (Pijn and da Silva, 1993). This is a more flexible method, while keeping the number of parameters reasonably low (too many parameters would lead to 'overfit' i.e. good description of any

relationship including noise). In reference to the  $r^2$  this non-linear measure has been named  $h^2$ . In practice, in a sliding window, a piecewise linear regression is performed between each pair of signals. The  $h^2$  is the coefficient of determination, which measures the goodness of fit of the regression (equivalent to the  $r^2$  used in linear regression). The  $h^2$  is bounded between 0 (no correlation) and 1 (maximal correlation) and is asymmetric. This method has been shown to be sensitive to: nonlinear relationships between signals (Lopes da Silva et al., 1989), phase-to-phase coupling (Wendling et al., 2009), amplitude-to-amplitude coupling (Wendling et al., 2009), signals generated by nonlinear systems and coupled linearly or nonlinearly (Wang et al., 2014; Wendling et al., 2009), asymmetric relationships between signals (Lopes da Silva et al., 1989), signals containing epileptic discharges generated by neural mass models (Wendling et al., 2009). Regarding the cross-frequency coupling, the  $h^2$  is usually calculated in broadband and is independent of the frequency, which does not allow to evaluate this aspect. However, it is theoretically possible to calculate it on sub-band filtered signals to evaluate the cross-frequency coupling, and in this case the results are close to those obtained with a linear correlation. Finally,  $h^2$  is not a particularly designed method for evaluating phase-amplitude coupling. Other methods that does not assume a linear relationship have been developed such as mutual information or transfer entropy (Bastos and Schoffelen, 2016) and have shown a good sensitivity to non-linear relationships (Wang et al., 2014).

Another important aspect is the distinction between methods that are computed from the time (e.g. correlation, cross-correlation, mutual information, transfer entropy) or frequency domain representation of the signals (e.g. coherence, phase locking value, phase slope index). For the latter, the equivalent of correlation in the frequency domain is coherence, introduced in the context of epilepsy by Brazier (Brazier and Casby, 1952). This measured

allows measuring the strength of linear coupling at different frequencies. The coherence measure (ranging between 0 and 1) is based on the Fourier transform, that decomposes each signal as a set of sine wave at different frequencies, each having an amplitude and a phase (temporal shift at a given frequency). The profile of amplitudes across frequencies is the spectrum. The coherence is simply the correlation of the Fourier coefficients across several time windows. Importantly, this requires averaging across several time windows – coherence between one time window and another one would be by construction 1. The coherence method assumes that signals are linked both in amplitude and frequency. This can be separated in a measure of amplitude correlations only and a measure of phase locking only (i.e. constant delays between signals at a given frequency across time windows, independently of the amplitude). To be noted, interictal signals containing transient patterns (e.g. interictal epileptiform discharges) may not be described well by stable sine waves of the Fourier transform. Thus, wavelet transform has been proposed, which is based on the non-stationary wavelet transform, and correlation can be applied to the wavelet coefficients (Amini et al., 2011).

One may be also interested in the direction of the flow of information in connectivity analyses and several methods have been developed to assess directionality (e.g. cross-correlation, granger causality, transfer entropy) whereas some others cannot estimate this feature (e.g. correlation, mutual information, coherence, phase locking value). One of the easiest ways for this estimation is to look to propagation delays and then compute the correlation for shifted versions of one signal with respect to the other. The shift with highest correlation is retained, together with the respective correlation value. This is cross-correlation, which is adapted when one signal is simply a delayed version of the other with

no transformation. Using non-linear correlation ( $h^2$ ), directionality could be estimated from both the delay of the shift maximising the  $h^2$  value and/or the asymmetry of the values (Wendling et al., 2001). Other methods have attempted to quantify the causal relationship between time series such as granger causality and transfer entropy. The principle underlying Granger causality can be described as follows: X “granger-causes” Y if Y is better modelled using both the past of X and the past of Y than only using the past of Y. This is a stronger statement than simple correlation. Indeed, if signals happen to be oscillations at a constant frequency, then granger causality will find that the relationship is low – one oscillation can be well predicted by its own past alone (this is also possible to detect in a repetition of the events where one would search for constant phase relationship, i.e. phase locking).

Another important methodological point in the estimation of functional connectivity is how to deal with the common input problem. Indeed, the functional interaction between a pair of signals could be caused by common input from a third source (that may have not been considered/sampled). To limit this problem, methods using multivariate analysis have been developed. Their principle is that information from all channels is taken into account when estimating the functional connectivity between any pair of channels (e.g. directed transfer function, partial directed coherence but also partial version of cross-correlation linear or not) (Astolfi et al., 2008, 2007, 2005; Florin et al., 2010).

### *Methodological Considerations*

In iEEG functional connectivity analyses several parameters may influence the results (algorithms and parameters used (Ansari-Asl et al., 2006; Wang et al., 2014), montage and reference used (Bartolomei et al., 1999; Bastos and Schoffelen, 2016), duration of the period

analysed (Chu et al., 2012; Goodale et al., 2019; Kramer et al., 2011; Wang et al., 2014), power spectrum of the signals (Müller et al., 2008), distance between recorded channels (Goodale et al., 2019; Lagarde et al., 2018; Warren et al., 2010), effect of the partial spatial sampling (Conrad et al., 2020) signal to noise ratio (Bastos and Schoffelen, 2016) and interictal epileptiform discharges (Bartolomei et al., 2013; Bettus et al., 2008)) and may lead to detection of spurious connectivity. It should be kept in mind during the interpretation of results (Figure 2). For more detail about methodological considerations see *Supplemental Data* and the reviews by (Bastos and Schoffelen, 2016; He et al., 2019).

### *Graph measures*

Connectivity measures across all channels of interest (that can in addition evolve with time) lead to high amount of data that can be potentially very complex to analyse. It is thus interesting to summarize these data using mathematical tool such as graph-theory. In this framework, channels (single contacts in monopolar or pairs of contact in bipolar montage) can be seen as nodes of a graph and the value of connectivity between these channels as the link (edge) between these nodes. The advantage of this representation is to summarize the specific properties of the studied network and help to analyse its topology. Topology analysis aims at quantifying the organisation of the network (nodes with dense connectivity, organisation of the connections between nodes, etc. *(for further details see (Fornito et al., 2015))*). Schematically, two types of measures have been proposed. The first type measures the way a node (or a set of nodes = zone) is integrated in the whole network (local topology). The second type measures the overall organisation of the network (global topology). Local topology includes several measures of “centrality”, *i.e.* the importance of a node in terms of

its connectivity to the rest of the nodes (highly or weakly connected = high or low centrality value). Several metrics could be used (e.g. degree, node strength, betweenness centrality, eigenvector centrality, etc.), each with its own advantage and inconvenient, that we will not detailed (interested reader may look at specific review (Fornito et al., 2015, 2013; Gleichgerricht et al., 2015; Vecchio et al., 2017)). In the case of directed functional connectivity measures, one can estimate ingoing and outgoing centrality of each node. Global topology gives the relation between short-range and long-range connections and then the efficiency of the whole network. For example, the small-world topology is characterized by an efficient balance with several short-range and some long-range connections. This is frequently seen in real life examples for many fields, for example transportation networks (the important nodes or 'hubs' are the large cities that connected with each other while smaller cities only need to be connected to the nearest hub), including brain organisation.

Graph theory allows simplifying the analysis of complex networks such as those of the human brain (Stam, 2004) and help the comparison between patients. However, an important point concerning the use of graph theory metrics in iEEG studies is the bias related to incomplete spatial sampling. Thus, when we refer to centrality or topology in these studies, we are not speaking in terms of absolute values (at the scale of the entire brain as can be explore by fMRI, EEG or MEG) but in terms of relative values within the sub-network of explored structures. These metrics nevertheless make it possible to rank the structures according to their degree of connectivity, and to appreciate the modifications of topology within a sub-network related to its epileptic character or not. Another important problem is the risk of biasing the estimates of these metrics since some structures can be oversampled in iEEG which, if we consider all possible connections, risks overestimating the centrality of

these structures. It is necessary to control this bias by limiting to one the value of connectivity between regions of interest before performing the graph theory analysis. The centrality metrics must be normalized (for example by the theoretical maximum of centrality) to take into account of difference in the number of sampled regions between patients. Moreover, not all centrality metrics are equally robust to the problem of incomplete sampling. It appears that the simplest ones (node strength) have good performance and some methods have been suggested to estimate the confidence interval of these metrics (Conrad et al., 2020).

### **3. Functional connectivity in the interictal state**

#### **3.1. Links between FC and epileptogenicity**

Table 1 synthesizes data from studies using ECoG and/or SEEG recordings, as described above.

#### **ECoG studies**

Several studies have investigated iEEG functional interictal connectivity in epilepsy using electrocorticography data (ECoG). Firstly, Towle and colleagues demonstrated areas of locally increased coherence on ECoG within / nearby the epileptic zone, mostly in patients with temporal lobe epilepsy (Towle et al., 1998). Following studies using a mix of ECoG and depth-electrodes within hippocampi confirmed greater interdependence between structures belonging to the epileptogenic zone as compared with structures in the non-involved zone



(Arnhold et al., 1999; Dauwels et al., 2009). Schevon and colleagues found areas of increased synchrony using several distinct functional connectivity measures (correlation, phase synchrony, coherence magnitude, granger causality) with stability over time, in a group of 9 patients (Schevon et al., 2007). In this study, authors found a strong overlap between the epileptogenic zone and areas of hypersynchrony for both ECoG and depth-electrodes and, using mean phase coherence, found areas of local hypersynchrony (between 2-5cm) with temporal stability across time. This suggested that an increase in local synchrony could be a marker of epileptogenicity. Nevertheless, the overlap was not always perfect and the hypersynchrony clusters were sometimes located at the edge of, and not within, the epileptogenic zone. Moreover, complete resection of areas of local hypersynchrony was associated with favourable surgical outcome. Ortega and colleagues described a cluster of local hypersynchrony within the temporal neocortex of patients with temporal lobe epilepsy explored using intraoperative ECoG (Ortega et al., 2008). In this study, authors failed to find a correlation between complete resection of the clusters of local hypersynchrony and surgical outcome. This could be explained by the fact that most of their patients benefited from anterior temporal lobectomy and that ECoG are mostly sensitive to the activity of lateral temporal neocortex. Wilke and colleagues also showed a change in betweenness centrality obtained with directed transfer function in gamma band within the epileptogenic zone (Wilke et al., 2011).

Finally, only one iEEG study by Warren and colleagues was able to compare data from patients with epilepsy to patients without epilepsy (implanted for refractory facial pain), using ECoG, linear correlation and mean phase coherence (Warren et al., 2010). This study demonstrated that functional connectivity i) between the epileptogenic zone and other non-epileptogenic areas and ii) between the non-epileptogenic areas was lower than the

corresponding connections in controls. These results suggested a disconnection of epileptogenic structures from non-epileptogenic structures and a decrease of connectivity within the non-epileptogenic cortices.

### **SEEG studies**

The ECoG recording technique has several limitations (limited spatial sampling, exclusion of mesial cortical and subcortical structures, relatively indirect recording of cortical activity, mostly unilateral sampling and, for some reports, recordings performed under anaesthesia for intraoperative ECoG). SEEG studies may overcome some of these limitations. A first set of SEEG studies used bilateral recordings with two depth electrodes implanted along the postero-anterior axis of both hippocampi in patients with mesio-temporal epilepsy for whom the question of bilateral epileptogenicity was raised. This type of implantation allows for comparison of epileptogenic *versus* non-epileptogenic mesio-temporal structures (hippocampus and amygdala mostly). Mormann and colleagues showed a local increase in synchrony (mean phase coherence) between the structures of the epileptogenic zone, in a group of 17 patients (Mormann et al., 2000). Following studies using same approach confirmed these findings (Arnhold et al., 1999; Dauwels et al., 2009) and showed a disconnection (lower strength and eigenvector centrality) of the epileptogenic zone from their contralateral analogous (Van Diessen et al., 2013)..

Other studies have then used more complete SEEG sampling typically including neocortical temporal and extratemporal cortices. Three studies compared connectivity across the mesio-temporal structures according to their epileptogenicity (patients with mesio-temporal

epilepsy compared to patients with extra-temporal epilepsy), using nonlinear analysis through the  $h^2$  method (Bettus et al., 2011, 2008)) or the synchronization likelihood (Bartolomei et al., 2013). Authors have found higher connectivity between these structures when they belong to the epileptogenic zone (Bartolomei et al., 2013; Bettus et al., 2011, 2008). A methodological question was to know the role of interictal spikes and whether they could increase connectivity values (Bartolomei et al., 2013; Bettus et al., 2008). However, the suppression of sections comprising interictal spikes did not change the results of both functional connectivity (Bettus et al., 2008; Jiang et al., 2022) and graph theory metrics (Bartolomei et al., 2013). Varotto and colleagues specifically addressing functional connectivity in patients with focal cortical dysplasia (FCD) type II estimated the role of the epileptogenic lesion itself (Varotto et al., 2012). They showed an increase in outgoing connections between 30-80Hz in FCD compared to other structures of the epileptogenic zone. Using measures of centrality from graph theory, this study also showed higher betweenness centrality values within the FCD.

We recently reported a study of interictal functional connectivity (non-linear correlation,  $h^2$ ) in a large series of 59 patients with various forms of focal epilepsies not limited to temporal epilepsies and with a broad SEEG sampling (Lagarde et al., 2018). In this study, the different epileptogenic networks were first defined as precisely as possible by quantifying the ictal activity recorded in SEEG thanks to the epileptogenicity index (Bartolomei et al., 2008). Thus, the epileptogenic networks were defined as Epileptogenic Zone (EZ), Propagation Zone (PZ) and Non-Involved Zone (NIZ) networks. Independently of the inter-contact distance, there was a gradual decrease of FC from the EZ (disclosing the highest connectivity) to the PZ (characterized by intermediate level of connectivity); and finally, to NIZ (with lowest connectivity). Moreover, the areas belonging to the EZ were preferentially connected with

the areas belonging to the PZ. The EZ were also more interconnected than connected to NIZ. This result confirmed the findings of previous studies showing a trend for a “disconnection” of the epileptogenic structures with the non-epileptic brain areas (Van Diessen et al., 2013; Warren et al., 2010). Our findings were consistent in broadband but also in frequency sub-bands. The directionality of connectivity (estimated from time delays) did not allow for identification of a significant leaders in broadband analysis, but the epileptogenic zone was found to be the leading zone in alpha and beta frequency bands. Goodale and colleagues confirmed our findings (Goodale et al., 2019) and found higher clustering coefficient, nodal betweenness centrality, and edge betweenness centrality for the epileptogenic areas. They also fitted a model in order to predict the epileptogenicity of structures based on connectivity measured and obtained an accuracy of 80.4% (sensitivity 82.5% and specificity of 60.4%). Narasimhan and colleagues extended these data using several methods for connectivity estimation: imaginary coherence, mutual information, partial directed coherence and directed transfer entropy (Narasimhan et al., 2020). The definition of the epileptogenic zone was not quantified in the study and not precisely defined, but authors found a gradual decrease of connectivity values from epileptogenic to propagation to irritative (defined as non-involved during seizure) and to non-involved zone. Looking at the predictive value of interictal connectivity to predict the epileptogenicity of the structures, authors found the best predictive value (AUC) for the three following methods (by decreasing performance): undirected mutual information, directed transfer function (DTF) and undirected imaginary coherence. Furthermore, the combination of connectivity measures improved the predictive value moderately (+4% on AUC). Notably, the model performed equally well in the subset of patients who were seizure-free after surgery (higher confidence in the exact definition of the epileptogenic zone). Recently, Paulo and colleagues

investigated the impact of time in EMU, changes in antiseizures medications doses, seizure burden, and differences between eyes-closed formal resting-state, and eyes-open pseudo-resting states on interictal SEEG FC (imaginary coherence and partial directed coherence computed in the alpha band) (Paulo et al., 2022). They confirmed that non-directed and inward connectivity measures are higher in EZ compared to NIZ, but most importantly demonstrated that: 1) FC measures are stable over time; 2) FC measures are not influenced by the seizure burden; 3) antiseizure medication dose may influenced some FC measures (imaginary coherence with smaller difference between EZ and NIZ in case of smaller dose of antiseizure medication) but not some other (partial directed coherence); 4) the type of resting-state (formal eyes-closed or not) may influence some FC measures (partial directed coherence with higher difference between EZ and NIZ during formal eyes closed resting state) but not some other (imaginary coherence). Finally, Jiang and colleagues looked specifically at the asymmetry of connectivity between EZ and NIZ (Jiang et al., 2022). They observed that resting-state information flows from NIZ to EZ across all frequencies and that FC measures remain stable across several periods of recording. Moreover, using cross-frequency coupling analyses they showed that information from NIZ high frequency activities lead EZ low frequency activity. Based on these features, authors found that a random forest classifier had an accuracy of 88% to predict the EZ.

These studies discussed above used a definition of the epileptogenic zone based on iEEG biomarkers (visual or quantified) and have of course an inherent limitation as these markers do not have a perfect performance. It is possible that in some cases, especially in non-seizure free patients, the epileptogenic zone has been misjudged. This is possibly suggested by some studies showing differences in connectivity according to the surgical outcome (*see below*). Thus, future studies focusing only on seizure-free patients after complete surgery of

their epileptogenic zone, thus with *a priori* a correct definition, would be useful to control this potential bias. To control this potential bias, some authors have also focused their analyses on an operational definition of the epileptogenic zone, namely the resection zone. Although this definition is pragmatic and close to clinical practice of epilepsy surgery, it has several disadvantages including: exclusion of non-operated patients (often more complex cases with wider epileptogenic zone and counting up to 50% of SEEG explored patients), inclusion of non-epileptogenic regions within this zone (e.g. anterior temporal lateral neocortex in standard anterior temporal lobectomy / lateral structures on the surgical access to mesial epileptogenic zone), and exclusion of some epileptogenic zones (e.g. located in eloquent cortices). Following such methodology, Park and Madsen demonstrated that interictal connectivity (estimated from Granger causality on a mix of depth-electrodes and ECoG recordings in 25 patients) predicts significantly better than chance the location of epileptogenic / resection zone (RZ) (Park and Madsen, 2018). Shah and colleagues have recently replicated this finding in a study on 27 patients recorded using a mix of ECoG and depth electrodes (with a majority of ECoG) (Shah *et al.*, 2019). An interesting method in this study is the normalisation by a spatially constrained null model. In line with previous findings, these authors showed a gradual decrease of connectivity values (edge weight) from: 1) connections within the resection zone (highest values), 2) connections linking resection and non-resection zones, and 3) connections within non-resection zone (lowest values).

Taken as a whole, data from SEEG studies demonstrated a higher connectivity of the EZ than NIZ and is relatively disconnected from the NIZ. These findings seem robust across time and method used. Moreover, the information from connectivity could be useful to locate the EZ.

## **Cortico-cortical evoked potentials studies**

Directed functional connectivity can also be estimated from cortico-cortical evoked potentials (CCEPs) generated by direct cortical electrical stimulation using intracranial electrodes (Boulogne et al., 2016; Trebaul et al., 2018). The foundations of this approach were laid more than 50 years ago when the Saint-Anne's team in Paris proposed to study the functional connections between the hippocampus and the amygdala from SEEG recordings (Buser et al., 1969). CCEPs consist in delivering bipolar single-pulse electrical stimulations in a given region and probing other regions for significant evoked potentials, that reflect actual anatomical connections between the stimulated and the responding regions (either direct or passing through synapses that delay the evoked response). CCEPs corresponds to early potentials beginning in the first 100 ms after the stimulation. From the presence or the absence of CCEP responses it is possible to infer the directed (and causal) connectivity between two areas and then to obtain a connectivity matrix.

Table 2 synthesizes data from studies using CCEPs to infer anatomo-functional / effective connectivity in iEEG recordings. Lacruz and colleagues failed to observed difference in the hemispheric CCEPs according to their epileptogenicity (Lacruz et al., 2007). However, following studies using more refined methodology achieved to observe connectivity differences according to the epileptogenic nature of the structures. For example, looking at centrality metric derived from CCEP, Keller and colleagues found higher in-degree in the seizure-onset-zone than outside (without difference in out-degrees) (Keller et al., 2014). Interestingly, Parker and colleagues reported results that are very close to SEEG studies demonstrating: 1) higher effective connectivity for the connections within epileptogenic

zone, in comparison with the connections within zones outside the epileptogenic zone; 2) higher outdegree and normalised outdegree for contacts belonging to the epileptogenic zone (Parker et al., 2018). Zhao and colleagues also confirmed higher connectivity within the epileptogenic zone in comparison with the non-epileptogenic zones, with significantly higher degree centrality and nodal shortest path length (not significant for betweenness centrality, clustering coefficient and local efficiency) (Zhao et al., 2019). It should be noted that, in these studies, the majority of other nodal graph theoretical parameters (in-degree, clustering coefficient, centrality) showed no significant difference between epileptogenic and non-epileptogenic contacts (Parker et al., 2018; Zhao et al., 2019), pointing out the importance of the choice of the centrality measure (Coito et al., 2019; Geier and Lehnertz, 2017). Following these studies, Guo and colleagues demonstrated in 25 patients recorded using SEEG electrodes that directed connectivity differs significantly between epileptogenic and non-epileptogenic zones after controlling for the inter-contact distance (Guo et al., 2020). They found a decrease of connectivity from intra-epileptogenic zone connections (with highest value); to “between epileptogenic and propagation zones”; to “intra-propagation zone connections”; to connections “between non-involved zone and propagation or epileptogenic zone”; to “intra-non-involved zone connections” (with the lowest value). Authors did not find significant directionality between zones (*e.g.*, no difference between connectivity values from epileptogenic to propagation zone connection values from, propagation to epileptogenic zone).

Overall, CCEPs studies confirmed findings from resting-state SEEG studies and demonstrated a higher connectivity of within EZ and PZ than within-NIZ.



### **3.2. Changes in network topology**

Varroto and colleagues found higher betweenness centrality (*i.e.* ratio between the number of shortest paths passing through a specific node and the total number of shortest paths in the network) within FCD type II than outside the lesion area (Varotto et al., 2012). Goodale and colleagues found also higher centrality metrics within the EZ (betweenness centrality and clustering coefficient, this latter reflecting the degree to which nodes tend to cluster together) (Goodale et al., 2019). Using CCEPs, Zhao and colleagues found higher degree centrality and shorter path length within the EZ (Zhao et al., 2019). Therefore, studies suggest higher centrality of the EZ. Bartolomei and colleagues, looking at the SEEG data of 11 patients with mesial temporal lobe epilepsy in comparison to 8 patients with non-mesial temporal lobe epilepsy, found an increase in the clustering coefficient and path length within the epileptogenic temporal lobe (Bartolomei et al., 2013). This result suggested a more regular organisation of the functional connectivity between temporal structures when they belong to the EZ. These studies suggest that some measures of centrality may be correlated with the degree of epileptogenicity of structures. However, the choice of the metric used seems crucial and future studies are needed.

### **3.3. Directionality of functional connectivity**

Several studies investigated the directionality of connectivity in order to identify the leading zone. This directionality could be estimated from causality method (Granger causality and its extensions as partial directed coherence (PDC), directed transfer function (DTF)) or using delays and/or asymmetry of non-linear correlation values. The literature in the domain is not

unanimous with some studies suggesting a leading role (higher out-connectivity) of the epileptogenic zone (Bettus et al., 2011; Lagarde et al., 2018; Varotto et al., 2012) and some others suggesting a higher inward connectivity toward the epileptogenic zone (Jiang et al., 2022; Narasimhan et al., 2020; Paulo et al., 2022; Vlachos et al., 2017). Moreover, using CCEPs, Parker and colleagues highlighted the higher outward connectivity of the epileptogenic zone (Parker et al., 2018) whereas Guo and colleagues did not find significant difference between inward and outward connectivity of the epileptogenic zone (Guo et al., 2020). These discrepancies could be due to variable methods used for connectivity estimation. To be noted, some studies using the same method, namely the partial directed coherence (PDC), have opposite results (Narasimhan et al., 2020; Paulo et al., 2022; Varotto et al., 2012). Another explanation could be the impact of interictal spikes on connectivity directionality, because some authors included spikes in their analyses (Bettus et al., 2011; Lagarde et al., 2018; Varotto et al., 2012) and others did not (Narasimhan et al., 2020; Paulo et al., 2022). Therefore, despite the relatively low effect of epileptic spikes on the overall connectivity value (Bartolomei et al., 2013; Bettus et al., 2008; Jiang et al., 2022; Park and Madsen, 2018), it is possible that spikes affect the directionality of connectivity (Karunakaran et al., 2017). Further studies looking at the effect of spikes and methods used for estimating the directionality of the connectivity of the epileptogenic zone are still needed.

### **3.4. Association with other variables**

Van Dellen and colleagues investigated the effect of epilepsy duration on functional connectivity (phase lag index) in temporal neocortex (van Dellen et al., 2009). They showed a

decrease in connectivity value with increase in epilepsy duration, and a more random configuration of the network (decrease of the clustering coefficient and of the small world index) in case of longer epilepsy duration. Authors did not find significant association for age at epilepsy onset and seizure frequency. Unfortunately, the information about the type of epilepsy (mesio-temporal or latero-temporal) and the type of surgery performed were not available in this study. It is therefore difficult to speculate on the precise epileptogenicity of the studied structures. Bartolomei and colleagues suggested that the topology of interictal networks evolves with time (Bartolomei et al., 2013). They observed an increase of the “small-worldness” (S index) with the increase in epilepsy duration (being essentially due to decrease of the path length over time).

While the pattern of connectivity changes during peri-ictal state (pre-, per- and post-ictal) is increasingly known ((Bartolomei et al., 2004; Courtens et al., 2016) , review in (Bartolomei et al., 2017)), few studies have focused on the temporal variation / dynamics of interictal functional connectivity measured from intracranial EEG recordings. Geier and Lehnertz has shown fluctuation of the degree of centrality of brain regions across long-term intracranial recordings on timescales of hours to days, with strong contributions of daily rhythms (Geier and Lehnertz, 2017). This study found differences in the variation across time of centrality metric between EZ and non-involved regions, with slightly higher variation for EZ. The amplitude of variation was also higher using betweenness centrality rather than strength centrality. However, Kramer and colleagues demonstrated the emergence of stable network pattern across long-term recordings (Kramer et al., 2011). Similarly, others studies have reported stability of the functional connectivity results across days of intracranial EEG recordings in patients with epilepsy (Dauwels et al., 2009; Jiang et al., 2022; Mormann et al., 2000; Paulo et al., 2022; Schevon et al., 2007). This result strengthens the confidence in the

use of connectivity data for EZ delineation purpose in practice. However, it remains unclear what could be the added value of the estimation of interictal functional connectivity dynamic into the delineation of the EZ and further studies on the topic are needed.

### **3.5. Association with surgical outcome**

Table 3 summarizes the data concerning the association between functional connectivity data and surgical outcome. Schevon and colleagues have first suggested a link between the level of interictal functional connectivity impairment and post-surgical prognosis (Schevon et al., 2007). Antony and colleagues analysed the functional connectivity (linear correlation) between mesio-temporal and neocortical structures in 23 patients operated for drug refractory temporal lobe epilepsy (Antony et al., 2013). They found that the smaller the mean and the variation of the connectivity values, the better the surgical outcome. The performance of connectivity data was very good (accuracy = 87%) for distinguishing patients categorized with favourable and unfavourable post-surgical outcome, but the association with the SEEG-defined epileptogenic zone was not formerly studied. In contrast, Goodale and colleagues suggest that patients with higher connectivity within the resection zone could have more favourable surgical outcome (Goodale et al., 2019).

Recently and in the same vein, Shah and colleagues found that patients with favourable outcome had higher within-resection zone (RZ) connectivity than patients with unfavourable outcome (Shah *et al.*, 2019). Moreover, the higher the overlap between the RZ and the nodes with the highest strength, the better the post-surgical seizure outcome. In addition, the distinction between patients with good or bad outcome was better using beta-

band connectivity. Nevertheless, the great variability of values across patients seems to preclude easy application at the individual level because of the difficulty to set a common threshold. A study using CCEPs to estimate directed functional connectivity, showed a positive correlation between the values of functional connectivity within the EZ and the surgical outcome (Guo *et al.*, 2020). These results are in line with a study using MEG showing that higher connectivity within the resection zone was associated with favourable outcome (Englot *et al.*, 2015). Looking at the directionality of the FC, Jiang and colleagues demonstrated that larger resting-state within-frequency information flow asymmetry between EZ and NIZ was associated with favourable seizure outcome (Jiang *et al.*, 2022). Interestingly using this information, a random forest classifier had an accuracy of 86% to predict surgical outcome.

In our above-mentioned study, we have suggested that a larger disturbance of cerebral connectivity (higher connectivity outside EZ and PZ, i.e., within-NIZ and between PZ-NIZ) is associated with worse prognosis (Lagarde *et al.*, 2018). Similar findings were recently reported using ECoG and betweenness centrality: patients not seizure-free after surgery had higher value of betweenness centrality (BC) in interictal and post-ictal period, and a greater proportion of extreme-valued BC nodes (Grobelny *et al.*, 2018). However, the individual predictive value of these connectivity measures on post-surgical prognosis is not yet known. Future studies may investigate how this connectivity data can be use in clinical practice in order to predict the chance of surgical success.

Overall, studies showed that the higher is the connectivity within the EZ and the larger is the difference with the connectivity of the NIZ, the better is the surgical outcome. The potential predictive value for surgical outcome obtained from presurgical connectivity has been also

reported in several works using tractography MRI data. It was suggested that pathologically increased limbic and extra-limbic structural connectivity can explain worse seizure outcome after epilepsy surgery (Bonilha et al., 2015, 2013), including a role of thalamocortical connectivity (He et al., 2017; Keller et al., 2015). Noteworthy, these studies reported better predictive value of connectivity than the sole usual clinical variables for post-surgical outcome (He et al., 2017; Keller et al., 2015; Morgan et al., 2019).

### **3.6. Connectivity changes induced by neurostimulation techniques**

Another important and growing field in epilepsy surgery is neurostimulation: vagal nerve stimulation, deep-brain stimulation, responsive neurostimulation (Fisher et al., 2010; Fisher and Velasco, 2014; Geller et al., 2017; Jobst et al., 2017; Ryvlin et al., 2021, 2014). Several studies have evaluated the impact of these techniques on intracranial EEG functional connectivity. Bartolomei and colleagues focused on VNS induced connectivity changes (comparison ON and OFF periods) in 5 patients explored by SEEG (Bartolomei et al., 2016). They found that non-responder patients exhibited increase in overall connectivity while the responder patients exhibited a decrease. These findings are in line with scalp EEG studies showing an association between the ability of VNS to decrease FC during ON periods and its efficacy (Bodin et al., 2015; Sangare et al., 2020). Moreover, VNS was able to induce some changes of connectivity within the EZ (increase in one non-responders patients and decrease in the responder one) (Bartolomei et al., 2016). Yu and colleagues focused on the effect of anterior thalamic nuclei (ANT) deep brain stimulation in 9 patients explored by SEEG (Yu et al., 2018). In this study, authors found that high-frequency stimulation of the ANT decreased

the connectivity of the brain networks during ON periods. In line with these results a recent study has shown that pulvinar stimulation can decrease the duration of temporal seizures and the associated alteration of consciousness (Filipescu et al., 2019), and that in responders stimulation leads to a decrease in synchrony between extratemporal brain regions (Deutschová et al., 2021).

These preliminary studies suggested that neuromodulation techniques may act also by modulating functional connectivity. Further studies investigating systematically the effect of different parameters of neuromodulation on large-scale SEEG connectivity under various and neurostimulation protocols would be interesting, in order to help choosing optimal parameters to use for VNS or DBS. This is especially important as different frequencies seem to induce different changes on connectivity (Bartolomei et al., 2016; Yu et al., 2018)).

## **4. COMPARISON WITH OTHER MODALITIES**

### **4.1. MRI**

Only a few studies have compared intracranial EEG and MRI functional connectivity. Bettus and colleagues compared functional connectivity as extracted from SEEG recordings with that obtained from fMRI (Bettus et al., 2011). This latter study reported some multimodal agreement: 1) in the directionality of connectivity: the epileptogenic zone (ZE) influenced the none-involved zone (NIZ); 2) in the decrease of functional connectivity between the EZ and the NIZ (delta band SEEG) and within the NIZ in fMRI. Nevertheless, there was some discrepancies with an increase in SEEG functional connectivity (in the beta band) in the EZ and secondary irritative zone (IZ2) while the BOLD functional connectivity was decreased in IZ2. These results can be explained by the fact that the two modalities do not study the same

processes, especially at different time scales. Ridley and colleagues looked at the comparison between functional connectivity recorded simultaneously in fMRI and SEEG (Ridley et al., 2017). They showed that there was a good intermodality correlation in non-epileptic areas but an alteration of this correlation in epileptic regions.

Besson and colleagues, focusing on the link between the structural connectivity alterations according to the brain network involved during seizure as defined by SEEG in patients with temporal lobe epilepsies, revealed that structural connectivity was significantly preserved within epileptic zones (epileptogenic and propagation zones) and decreased in non-epileptic structures (Besson et al., 2017). Taken together with other structural connectivity MRI studies, these findings suggest that : 1) areas involved in seizure generation and propagation (e.g. thalamus in temporal lobe epilepsy) have relatively preserved (higher) structural connectivity (Besson et al., 2017; Bonilha et al., 2012; Dinkelacker et al., 2015); and 2), other remote areas have widely decreased structural connectivity (Besson et al., 2014). This pattern of local ‘hyperconnectivity’ within epileptic structures combined with widespread ‘hypoconnectivity’ outside these areas is concordant with iEEG findings and other studies on functional connectivity extracted from non-invasive electrophysiological recording (*see below*). This similarity confirms both the tight relationships between structural and functional connectivity known to exist in healthy conditions (Goni et al., 2014; Honey et al., 2007), and the increased structural-functional correlation in epilepsy (Wirsich et al., 2016).



## 4.2. MEG/EEG

MEG studies have demonstrated an increase in functional connectivity between regions within the epileptogenic zone network (Englot et al., 2015; Juárez-Martínez et al., 2018; Nissen et al., 2016; Wu et al., 2014) associated with a decrease in functional connectivity between these regions and other non-involved brain regions (Englot et al., 2015; Nissen et al., 2016). Interestingly, Englot and colleagues (source-space MEG connectivity) found that the degree of global reductions in functional connectivity were related to epilepsy duration and frequency of consciousness-impairing seizures, and thus may reflect the deleterious effects of seizures on brain networks over time (Englot et al., 2015). Moreover, in this study, the increased regional connectivity appears to be a marker of favourable seizure outcome after surgery. Changes in network topology have also been identified in MEG (Chavez et al., 2010; Horstmann et al., 2010), in particular an increase in the betweenness centrality in the network of epileptogenic regions (Nissen *et al.*, 2017, 2018). Nevertheless, the correlation between MEG and iEEG connectivity seems limited, as well as the ability of connectivity results to distinguish between resection areas and non-resection areas (Juárez-Martínez et al., 2018; Nissen et al., 2018). These discrepancies could be due to the metrics used to analyse connectivity (Coito et al., 2019) and further studies are needed.

Some scalp EEG studies have shown a decrease in the influence (in terms of out-connections) of the default mode network, and an increase of in-connections into the epileptic hippocampus in patients with temporal lobe epilepsy (Coito *et al.*, 2016). Coito and colleagues used high-density EEG and source-space functional connectivity in IED-s-free epochs (60s). They demonstrated that patients had a significantly reduced connectivity

within regions belonging to the default-mode network. Moreover, strongest connections arose from posterior cingulate cortex in controls and from the epileptic hippocampus in patients. Noteworthy, the connectivity results differ according to the disease duration, the cognitive (learning deficit) and psychiatric status (depression or not). Using similar methodology in epochs without interictal epileptiform discharges (IEDs), Verhoeven and colleagues applied two-class Random Forests classifiers on functional connectivity and were able to differentiate healthy control from patients and left from right temporal lobe epilepsy (TLE), at the individual level (Verhoeven et al., 2018). The classification achieved a high accuracy, sensitivity, and specificity (between 85% and 95%). As in the previous study by Coito and colleagues (Coito et al., 2015), the most important features for diagnosis were the outflows from left and right medial temporal lobe. However, it was important to consider the whole connectome (i.e., including connectivity values of several brain areas in the predictive model) to achieve correct classification.

Overall functional connectivity data from non-invasive recordings techniques (EEG, MEG) confirmed higher connectivity within EZ and highlighted the widespread hypoconnectivity outside the EZ.

### **4.3. Summary**

Taken as a whole, the data about connectivity from iEEG studies and from whole-brain non-invasive modalities (especially MEG (Englot et al., 2015) and structural MRI data (Besson et al., 2017)) suggested that focal refractory epilepsies are associated with a global profile of large-scale network alteration including: 1) a wide decrease of connectivity outside the EZ; 2)

an EZ exhibiting, rather than an increase, a relative preservation of its intrinsic connectivity (Figure 3); 3) an EZ with a preferential connection to PZ and with a relative disconnection from NIZ.

## **5. FROM EXCITABILITY TO CONNECTIVITY: CONCEPTUAL COMMENTS**

While most historical works have focused on the importance of the hyperexcitability of epileptic areas, it is increasingly apparent that the underlying connectivity is also essential for understanding the organization of interictal events and seizures. This hypothesis was suggested early on by Wendling and colleagues using a computational model (Wendling et al., 2005, 2001). The authors showed that the interictal-ictal transition was not explained solely by the excitation/inhibition balance but rather by the interactions between pyramidal cells and interneuron populations. Noteworthy, this concept has also been highlighted in experimental models (in vivo and in vitro), some authors have demonstrated how specific changes in the topology or synaptic strength can impact brain epileptogenicity (Morgan and Soltesz, 2008; Netoff et al., 2004). It has also been shown that a minor change in the topology of a network can explain the emergence of explosive changes in synchrony as observed during the generation and propagation of epileptic seizures (Wang et al., 2017).

Phenomenological model has shown that the network's ability to generate seizures is highly dependent on its topology. Hebbink and colleagues have demonstrated that: 1) even in the presence of a hyperexcitable node, some networks do not generate seizure; 2) the existence of a driving node greatly increases the number of seizures; 3) the presence of reciprocal connections between two nodes could act as a stabilizer reducing the number of seizures (Hebbink et al., 2017). Proix and colleagues, using a different phenomenological model (Jirsa

et al., 2014), systematically explored the impact of excitability and coupling values on the behaviour of two oscillators mimicking the activity of two brain regions (Proix et al., 2014). Variations in these two parameters were sufficient to induce different behaviours: 1) systematic seizure propagation, 2) partial seizure propagation, 3) change in the seizure-generating area across time, 4) lack of seizure propagation, and 5) lack of seizure genesis. This study has clearly demonstrated that both excitability and coupling of brain structures determine the behaviour of epileptic network. These concepts were recently confirmed in studies demonstrating that the dynamics of focal seizures is related to the underlying structural connectivity and that seizure spread is tightly controlled by structural connections (Proix et al., 2017; Shah et al., 2019a). This principle is used in large-scale seizure modelling called “virtual epileptic patient” (VEP) that is a whole-brain model (based on the architecture of the “virtual brain”) using the structural connectivity of the patient coupled with a neural mass model, able to reproduce epileptic seizure dynamics (Jirsa et al., 2017, 2014) and to simulate the pattern of seizure spread. Interestingly this model was able to reproduce *in silico* the spatio-temporal dynamics of seizure evidenced in SEEG at the patient level (Jirsa et al., 2017; Makhalova et al., 2022; Proix et al., 2018, 2017).

## **6. CONCLUSIONS AND PERSPECTIVES**

The different studies reviewed in this article were performed mainly with the aim of discriminating the EZ from less epileptogenic regions from invasive EEG data. Our results as well as data from the literature suggest a potential interest to distinguish the EZ from other areas (Narasimhan et al., 2020). In fact, an important point from our data (Lagarde et al., 2018) is the small difference in connectivity strengths between EZ and PZ. This observation

makes it difficult for connectivity methods to distinguish between epileptogenic and propagation zones, a classic goal of the pre-surgical workup. However, it suggests that there is probably more of a gradient of epileptogenicity than a true “clear cut” difference between these regions. Furthermore, because EZ have high intrinsic connectivity but low connectivity to nonepileptic areas, centrality measures (obtained by averaging the connectivity values of these two types of connections) may be insufficient to accurately determine EZ. Thus, the use of other markers may be relevant (e.g. directionality). Indeed, the literature suggests that only the EZ behaves as a "module" (higher connectivity within the EZ than between the EZ and other areas) (Lagarde et al., 2018), and then some specific graph-theoretic metrics could be markers to be tested in further studies. In addition, the added value of markers from connectivity analyses compared to classical markers of epileptogenicity such as ictal (e.g., epileptogenicity index (Bartolomei et al., 2008)) and interictal (e.g., spikes, HFO (Roehri and Bartolomei, 2019)) neuromarkers could also be investigated.

Moving forward, several studies have recently examined the value of simulation/modelling methods in surgical decision making. Most studies used ictal / peri-ictal ECoG data (An et al., 2019; Goodfellow et al., 2016; Junges et al., 2019; Khambhati et al., 2016; Kini et al., 2019; Lopes et al., 2018, 2017; Müller et al., 2018; Olmi et al., 2019; Steimer et al., 2017) and only one used inter-ictal ECoG data (Sinha et al., 2017). Further studies examining the added value of this simulation/modelling techniques in surgical decision making based on interictal SEEG functional connectivity data could be useful.

Further study could also consider performing connectivity analysis over IED-centred time windows and especially looking at directionality (Bou Assi et al., 2020). Such an analysis could add information about the differences between spikes inside and outside the EZ and

help to delineate the EZ more effectively from the interictal period. The goal would be to find markers of epileptogenicity from spike propagation. These methods could be compared to results obtained from co-occurrences (Bourien et al., 2005; Lambert et al., 2017; Malinowska et al., 2014), which have proven to identify interictal spike networks.

## **Funding statement**

Some of the discussed studies, from our team, and this review has been carried within the following grants: FHU EPINEXT and DHU-Imaging, A\*MIDEX project (ANR-11-IDEX-0001-02) funded by the "Investissements d'Avenir" French Government program managed by the French National Research Agency (ANR); "VIBRATIONS" ANR-13-PRTS-0011-01, funded by Agence Nationale de la Recherche (ANR) and Direction Générale de l'Offre de Santé (DGOS); European Union's Horizon 2020 research and innovation programme (grant agreement No 855109; ERC-SyG 2019) funded by the European Research Council (ERC).

## **Author Disclosure Statement:**

None of the authors has any conflict of interest to disclose

## **Author Contribution statement:**

Stanislas Lagarde performed the literature review, drafted the manuscript, and created the tables and figures. Christian-G Benar, Fabrice Wendling and Fabrice Bartolomei contributed to the writing of the manuscript, including its critical review. All authors approved the final form of the manuscript.

## **Ethical publication statement**

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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## TABLES

**Table 1: Summary of Studies on interictal functional connectivity using iEEG**

Studies are presented in chronological order. If the definition of the epileptic areas (epileptogenic, seizure onset zone, etc ...) is variable from one study to another, for simplicity we summarised the data with the terms epileptogenic zone (EZ) and non-involved zone (NIZ). For studies using ECoG recordings we precise if the recordings were performed during surgery procedure (with anaesthesia) or long-term monitoring.

*ECoG: electrocorticography; SEEG: stereo-EEG; EZ: epileptogenic zone; PZ: propagation zone; NIZ: non-involved zone; TLE: temporal lobe epilepsy; FCD: focal cortical dysplasia; NDT: neurodevelopmental tumour; Irritative zone: area with interictal spikes but no ictal discharge; RZ: resection zone.*

| Authors                          | Population  | Recording Modality   | Methods              | Main results   |
|----------------------------------|---|--|----------------------|--|
| <b>ECoG +/- depth electrodes</b> |   |  |                      |  |
| Towle et al., 1998               | 25 patients<br>Tumours in the sensory- motor region or temporal lobectomy | ECoG<br>During surgery<br>(5 with also pre-surgical recording) | Coherence            | Local zone of increase FC nearby/within EZ                     |
| Arnhold et al., 1999             | One patient with mesial TLE<br>One patient with neocortical epilepsy      | ECoG + depth electrodes<br>(During presurgical monitoring)     | "Interdependence"    | Greater FC within the EZ than within the NIZ                   |
| Schevon et al., 2007             | 9 patients with neocortical epilepsy                                      | ECoG<br>(During presurgical)                                   | Mean phase coherence | Area of local hypersynchrony (stable in time) overlapping with |

|                              |  |  |   |   |
|------------------------------|--|--|---|---|
|                              |  | <i>monitoring)</i>   |   | the EZ  |
| Ortega <i>et al.</i> , 2008  | 29 patients with TLE   | ECoG<br>(During surgery)                                   | Linear correlation, mutual information, and phase synchronization                                       | Cluster of local hypersynchrony in the epileptic temporal lobe ( <i>no good correlation with the epileptogenic zone</i> ) |
| Dauwels <i>et al.</i> , 2009 | 6 patients with neocortical epilepsy                                   | ECoG + depth electrodes<br>(During presurgical monitoring) | Cross-correlation, granger causality (directed transfer function), phase synchrony, magnitude coherence | Area of hypersynchrony correlate with the EZ  |
| Warren <i>et al.</i> , 2010  | Comparison of patients with chronic pain (n=2) and with epilepsy (n=4) | ECoG<br>(During presurgical monitoring)                    | Linear correlation, mean phase coherence  | Disconnection of EZ from the NIZ and decrease of connectivity within the NIZ  |
| Wilke <i>et al.</i> , 2011   | 25 patients with neocortical epilepsy                                  | ECoG<br>(During presurgical monitoring)                    | Directed transfer function ( <i>gamma band</i> )  | Correlation between “active node” and EZ<br><br>( <i>lower than interictal spikes</i> )                                   |
| Park and Madsen, 2018        | 25 patients (10 TLE)   | ECoG + depth electrodes                                    | Granger causality   | FC predicts better than chance the EZ / RZ  |
| Shah <i>et al.</i> , 2019    | 27 patients (18 TLE)   | ECoG + depth electrodes                                    | Linear Correlation  | Gradual decrease of FC: within-RZ > RZ-OUT > within-OUT   |
| <b>SEEG</b>                  |  |  |   |   |
| Mormann <i>et al.</i> , 2000 | 17 patients with TLE   | SEEG<br>(Bilateral   | Mean phase coherence  | Increase FC in the epileptogenic side   |

|                                  |  |   |                                 |  |
|----------------------------------|--|---|---------------------------------|--|
|                                  |  | <i>temporal mesial sampling)</i>                    |                                 |  |
| Bettus <i>et al.</i> , 2008      | 21 patients with mesial TLE + 14 with non-mesial TLE | SEEG  | Nonlinear correlation ( $h^2$ ) | FC within mesio-temporal structures is higher when these structures belong to EZ   |
| Bettus <i>et al.</i> , 2011      | 5 patients with TLE                                  | SEEG  | Nonlinear correlation ( $h^2$ ) | Higher FC within the EZ and the irritative zone than within the NIZ ( <i>in beta only</i> )<br><br>Leading role of the EZ  |
| Varotto <i>et al.</i> , 2012     | 10 patients with FCD II (neocortical epilepsy)       | SEEG  | Partial directed coherence      | Increase in outgoing connections (30-80Hz) in FCD compared to other structures of the epileptogenic zone<br><br>Increase in the betweenness centrality within the FCD. |
| Van Diessen <i>et al.</i> , 2013 | 12 patients with TLE                                 | SEEG<br><i>(Bilateral temporal mesial sampling)</i> | Phase Lag Index                 | Disconnection of the epileptogenic mesio-temporal structures from their contralateral non-epileptogenic homologous   |
| Bartolomei <i>et al.</i> , 2013  | 11 patients with mesial TLE + 8 with non-mesial TLE  | SEEG  | Synchronization likelihood      | FC within temporal structures is higher when these structures belong to EZ   |
| Lagarde <i>et</i>                | 59 patients with FCD                                 | SEEG  | Nonlinear                       | Gradual decrease   |

|                                 |                      |      |  |   |
|---------------------------------|----------------------|------|--|---|
| <i>al.</i> , 2018               | or NDT (20 TLE)      |      | correlation ( $h^2$ )  | <p>of FC: EZ &gt; PZ &gt; NIZ</p> <p>FC between EZ-PZ &gt; PZ-NIZ</p> <p>Leading role of the EZ</p>   |
| Goodale <i>et al.</i> , 2019    | 15 patients (12 TLE) | SEEG | Imaginary coherence  | <p>FC in EZ and EZ-NIZ higher than NIZ</p> <p>Higher clustering coefficient, betweenness centrality within EZ</p> <p>Predictive accuracy = 80.4%</p>                                    |
| Narasimhan <i>et al.</i> , 2020 | 25 patients (18 TLE) | SEEG | Mutual information, Imaginary coherence, Partial Directed Coherence, Directed Transfer Entropy | <p>Gradual decrease of FC: EZ &gt; PZ &gt; Irritative zone &gt; NIZ</p> <p>EZ with higher inward FC</p> <p>Predictive accuracy = 88%, better if combination of connectivity methods</p> |
| Paulo <i>et al.</i> , 2022      | 32 patients (18 TLE) | SEEG | Imaginary coherence, Partial Directed Coherence (in alpha band)                                | <p>Stability across time (days)</p> <p>Higher FC in EZ than in NIZ</p> <p>This difference decreased with the antiseizure medication withdrawal when using imaginary coherence</p>       |
| Jiang <i>et al.</i> ,           | 27 patients (23 TLE) | SEEG | Directed transfer function, cross-   | Higher inward strength in EZ  |



|      |  |  |                             |   |
|------|--|--|-----------------------------|---|
| 2022 |  |  | frequency<br>directionality | than in NIZ<br>Information flow<br>from NIZ high<br>frequency activity<br>to EZ low<br>frequency activity |
|------|--|--|-----------------------------|---|

**Table 2: Summary of studies on connectivity using Cortico-Cortical Evoked Potential (CCEP)**

Studies are presented in chronological order

*FC: functional connectivity; EZ: epileptogenic zone; NIZ: non-involved zone; PZ: propagation zone. SEEG: stereo-EEG; ECoG: electrocorticography; TLE: temporal lobe epilepsy*

| Authors                     | Population                           | Recording's modality  | Main results  |
|-----------------------------|--------------------------------------|---|---|
| Lacruz <i>et al.</i> , 2007 | 51 patients                          | ECoG + depth electrodes<br>( <i>Frontal and temporal recordings</i> ) | No difference in ipsilateral and contralateral hemispheric CCEP according to the side of the EZ |
| Keller <i>et al.</i> , 2014 | 15 patients (10 TLE)                 | ECoG + depth electrodes   | Higher in-degree in EZ<br>(no difference in out-degree)   |
| Parker <i>et al.</i> , 2018 | 7 patients with neocortical epilepsy | SEEG  | Higher FC within-EZ than within-NIZ<br>Higher outdegree of EZ                                   |
| Zhao <i>et al.</i> , 2019   | 8 patients (3 TLE)                   | ECoG<br>( <i>During presurgical monitoring</i> )                      | Higher FC of EZ > NIZ<br>Higher degree centrality and shorter path length of EZ                 |
| Guo <i>et al.</i> , 2020    | 25 patients (10 TLE)                 | SEEG  | Gradual decrease of FC: within-EZ > between EZ-PZ > within-PZ > between EZ-NIZ and PZ-NIZ >     |

|  |  |  |   |
|--|--|--|---|
|  |  |  | within-NIZ<br><br>No difference in directionality |
|--|--|--|---|

**Table 3: Links between functional connectivity data and post-surgical seizure outcome**

Studies are presented in chronological order

For studies using ECoG recordings we precise if the recordings were performed during surgery procedure (with anaesthesia) or long-term monitoring.

*FC: functional connectivity, ECoG: electrocorticography; SEEG: stereo-EEG; RZ: resection zone;*

*EZ: epileptogenic zone; TLE: temporal lobe epilepsy*

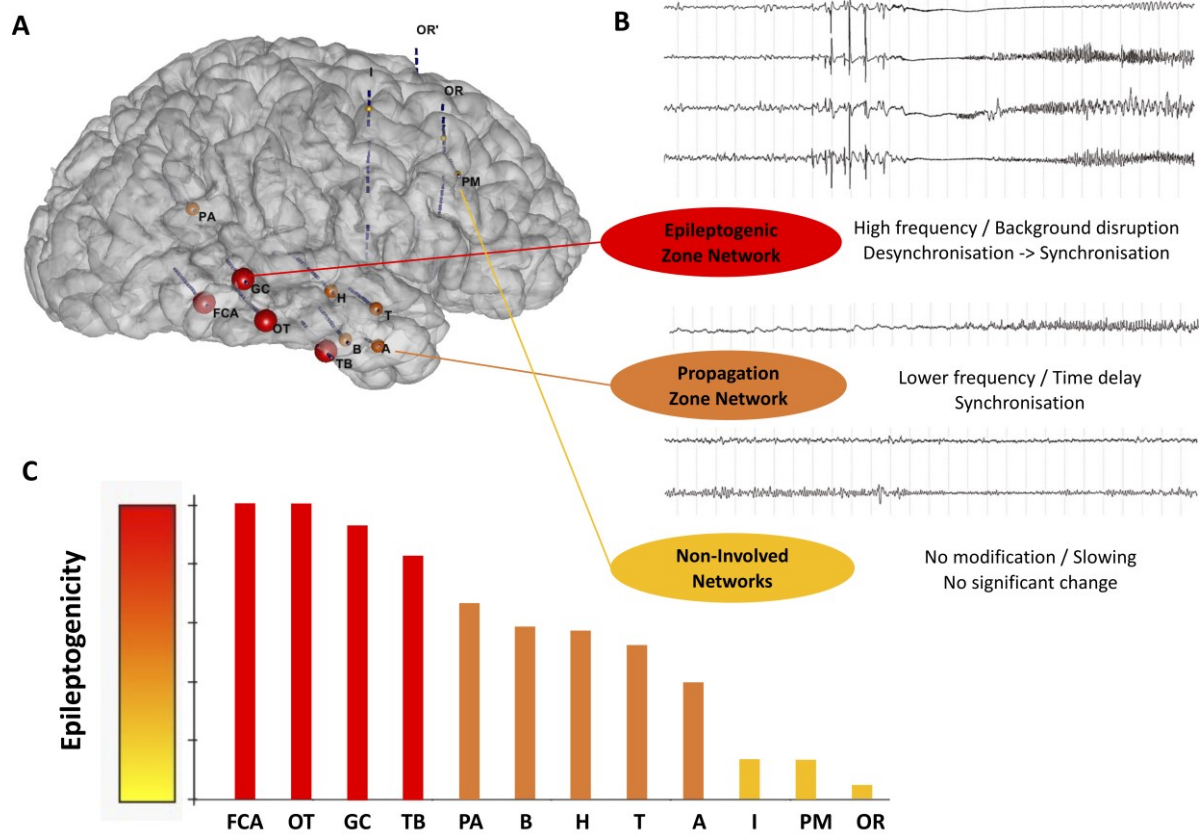
| Authors              | Population                           | Recording modality                      | Methods   | Main results   |
|----------------------|--------------------------------------|---|---|--|
| Schevon et al., 2007 | 9 patients with neocortical epilepsy | ECoG<br>(During presurgical monitoring) | Mean phase coherence  | Complete resection of area of local hypersynchrony associated with good outcome                        |
| Ortega et al., 2008  | 29 patients with TLE                 | ECoG<br>(During surgery)                | Linear correlation, mutual information, and phase synchronization | No correlation between complete resection of cluster of local hypersynchrony and post-surgical outcome |
| Antony et al., 2013  | 23 patients with TLE                 | SEEG                                    | Linear correlation  | Better outcome if weaker overall FC and more homogenous overall FC (less outlier with high             |

|                               |                                      |   |   |  |
|-------------------------------|--------------------------------------|---|---|--|
|                               |                                      |   |   | FC)  |
| Lagarde <i>et al.</i> , 2018  | 59 patients with FCD or NDT (20 TLE) | SEEG                                    | Nonlinear correlation ( $h^2$ )                                 | Worse outcome is higher FC within-NIZ  |
| Grobelny <i>et al.</i> , 2018 | 36 patients                          | ECoG<br>(During presurgical monitoring) | Granger causality   | Worse outcome if higher overall betweenness centrality and more outlier with high values                                 |
| Goodale <i>et al.</i> , 2019  | 15 patients (12 TLE)                 | SEEG                                    | Imaginary coherence   | Better outcome if higher FC within-RZ  |
| Shah <i>et al.</i> , 2019     | 27 patients (18 TLE)                 | ECoG + depth electrodes                 | Linear Correlation  | Better outcome if higher FC within-RZ<br><br>Better outcome with higher overlap between RZ and nodes with the highest FC |
| Guo <i>et al.</i> , 2020      | 25 patients (10 TLE)                 | SEEG                                    | CCEP  | Better outcome if higher FC within-EZ  |
| Paulo <i>et al.</i> , 2022    | 32 patients (18 TLE)                 | SEEG                                    | Imaginary coherence, Partial Directed Coherence (in alpha band) | No difference in EZ FC between patients being Engel I or not   |
| Jiang <i>et al.</i> , 2022    | 27 patients (23 TLE)                 | SEEG                                    | Directed transfer function, cross-frequency directionality      | larger within-frequency information flow asymmetry between EZ and NIZ is associated with favourable outcome              |

## FIGURES

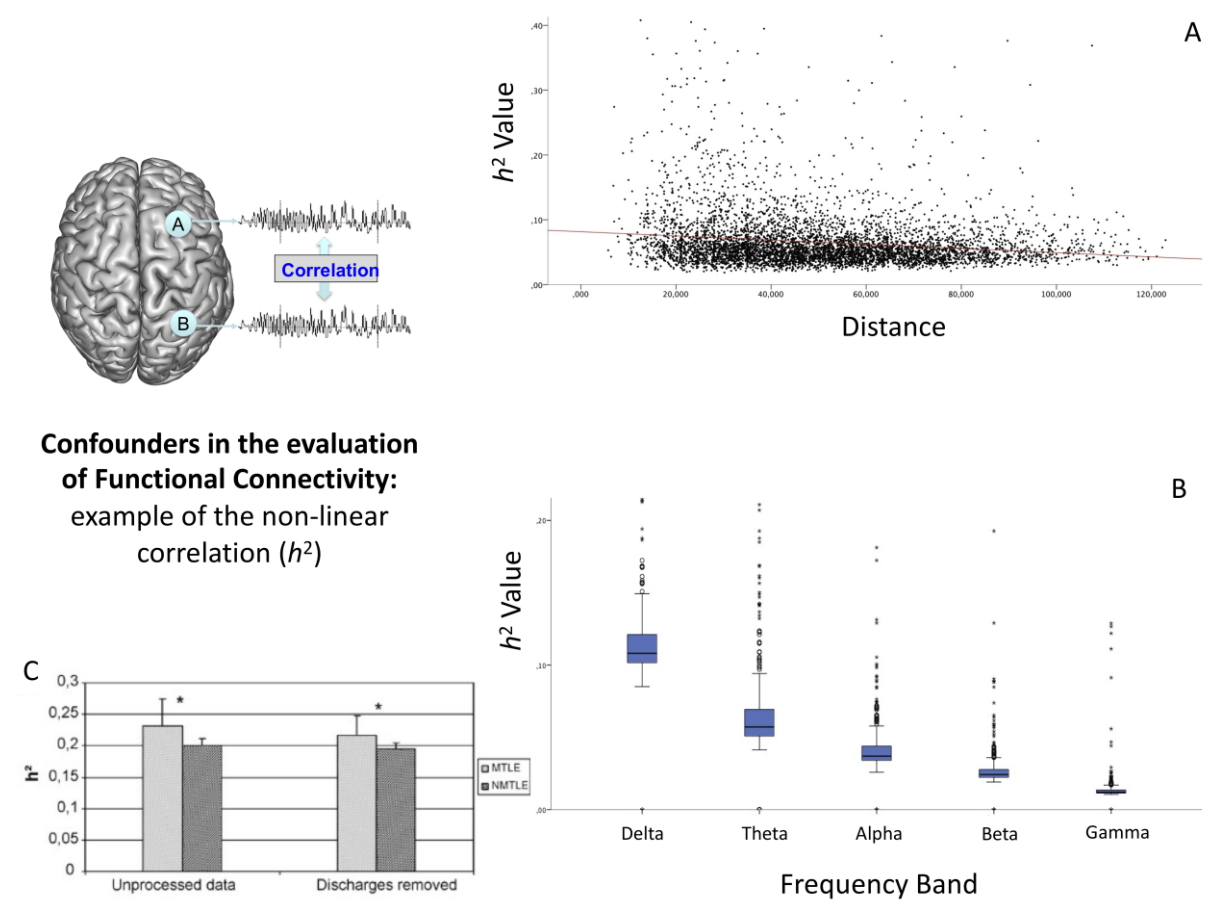
**Figure 1** represents a seizure recorded in SEEG where we observe a simultaneous co-implication of several distinct/distant cerebral areas at the time of the initiation and the propagation of the seizure. The frequent observation of this simultaneous involvement of a "network" of brain areas during seizures, as well as the connectivity changes observed at the time of the seizures (*not shown here*), led us to propose the concept of the three "networks": epileptogenic zone network (EZN), propagation zone network (PZN) and non-involved zone network (NIN).

- A) 3D representation of the epileptogenicity of the sampled area in a patient with SEEG recordings. Epileptogenic zone network (EZN) are the nodes with big red sphere, Propagation zone network (PZN) are the nodes with medium orange sphere, and Non-Involved zone network (NIN) are the nodes with small yellow sphere.
- B) Example of SEEG traces during a seizure within the epileptogenic (EZN), propagation (PZN) and non-involved zones (NIN) networks; and summary of the most frequent observed changes within each zone in term of signal properties
- C) Bar plot of the level of epileptogenicity for the nodes sampled in this example, showing a gradual decrease of epileptogenicity (FCA: right middle temporal gyrus posterior part; OT: right middle temporal gyrus posterior part; GC: right superior temporal gyrus posterior part; TB: right inferior temporal gyrus anterior part; PA: right angular gyrus; B: right middle temporal gyrus anterior part; H: right *planum temporale*; T: right *planum polare*; A: right middle temporal gyrus anterior part; I: right middle frontal gyrus posterior part; PM: right middle frontal gyrus anterior part; OR: right superior frontal gyrus posterior part).



**Figure 2** illustrates the confounders influencing the estimation of functional connectivity through the example of the non-linear correlation coefficient ( $h^2$ )

- A) The connectivity value decrease with the increase of inter-contact distance (possible solution: normalisation by the distance (using non-involved zone data) / multivariate analysis using the distance-effect)
- B) The connectivity values are lower for higher frequencies (possible solution: sub-bands analysis / comparison of the frequency content before analysis)
- C) The IEDs (unprocessed data) increase slightly the connectivity value without changing the global trend of difference between zones (higher connectivity when mesio-temporal structures are epileptogenic MTLE versus non epileptogenic NMTLE)

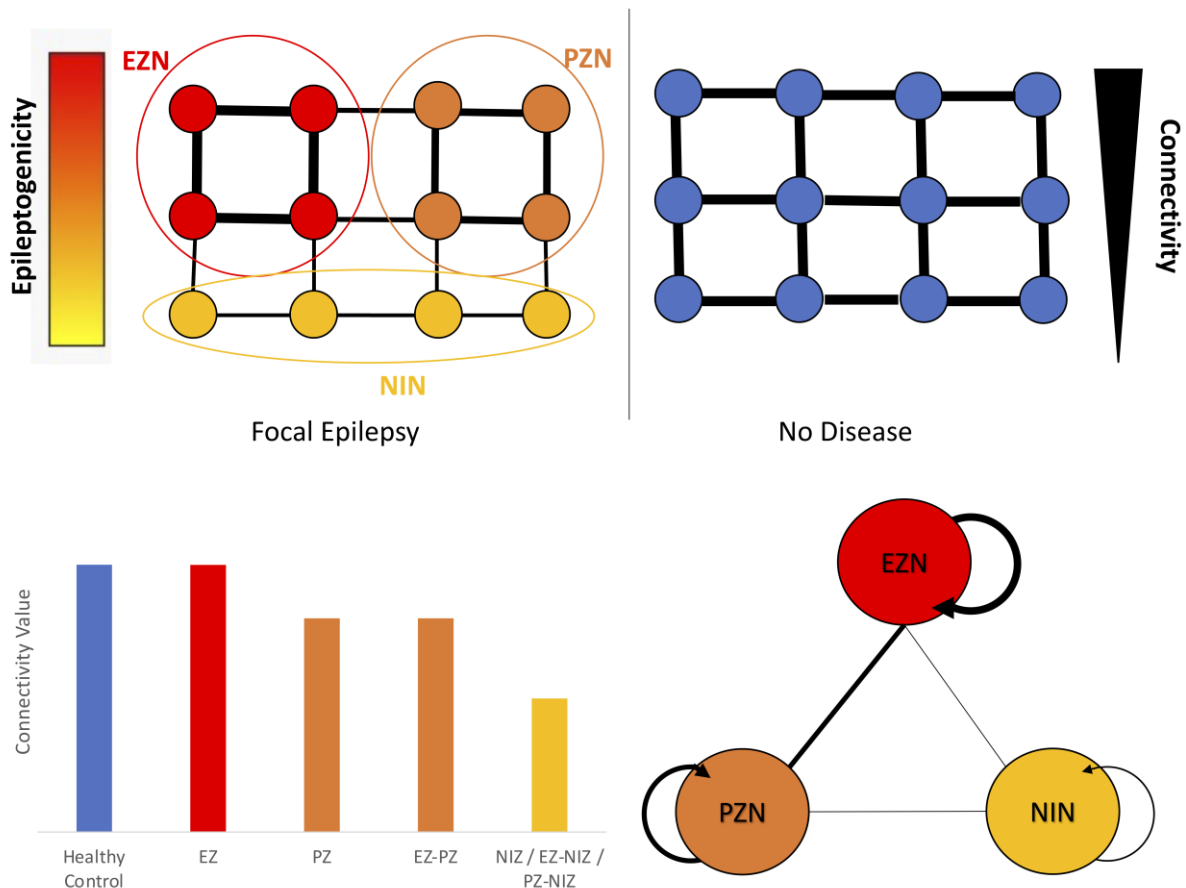


**Figure 3** synthesizes the main data on interictal functional connectivity.

In comparison with healthy control, epileptogenic zone network (EZN) shows a relatively preserve connectivity while non-involved zone network (NIN) has a decrease connectivity. Propagation zone network (PZN) shows an intermediate level of connectivity. Epileptogenic zone network (EZN) is preferentially connected to the propagation zone network (PZN) and relatively disconnected of the non-involved zone network (NIN).

For the clarity of the figure, all nodes are not inter-connected, and the connectivity is considered as equal between nodes in healthy condition (*it is not the case in human brain*).

The directionality is not represented in this graph as the existing data are contradictory on the role of the epileptogenic zone: sender or receiver?



## ***SUPPLEMENTAL MATERIAL***

### **METHODOLOGICAL ISSUES**

In iEEG functional connectivity analyses several parameters may influence the results and should be kept in mind during the interpretation of results (Figure 2).

#### **7. Algorithms to estimate functional connectivity**

Several algorithms to estimate functional connectivity exist and their choice could be difficult. In a study looking at the estimated synchronization between left and right hemisphere using intracranial-electroencephalographic (EEG) and testing various synchronization measures (nonlinear interdependence, phase synchronization, mutual information, cross correlation, and coherence), authors found that, except mutual information, all these measures give a useful quantification and despite their conceptual differences, results are qualitatively the same (Quiñero Quiroga *et al.*, 2002). Another comparative study using computational modelling and estimating various combination of models and synchronization methods confirms these findings showing that although results may differ from one method to the other, qualitatively their results are similar (Ansari-Asl *et al.*, 2006). Furthermore, (Wendling *et al.*, 2009) compared the performance of three families of connectivity methods (regression, phase synchrony and general synchronization) using simulations from various models in which a coupling parameter can be tuned. In this study,



none of the studied methods gave better results than the other ones in all simulated situations. However, regression methods ( $R^2$  and  $h^2$ ) were sensitive to the coupling parameter with average or good performances across situations. Moreover, in some situations, coherence and phase synchrony methods were not very sensitive to the increase of the coupling parameter (typically in amplitude coupling models where the interdependence between signals is not determined by a phase relationship).

Moreover, in studies in human, the performance across methods of connectivity estimation are similar with good correlation between them: mutual information, generalized synchronization, phase synchronization and linear correlation (Kraskov, 2004); phase synchrony, magnitude coherence, granger causality and linear correlation (Dauwels *et al.*, 2009); linear correlation, mutual information and phase synchronization (Ortega *et al.*, 2008); linear correlation and mean phase coherence (Warren *et al.*, 2010); and imaginary coherence, mutual information, partial directed coherence (PDC) and directed transfer entropy (DTF) (Narasimhan *et al.*, 2020) in all studies using intracerebral EEG data in human. However, for intracranial EEG several works have demonstrated the interest and the good performance of non-linear correlation analysis, probably because of the non-linear nature of iEEG signals especially within the EZ (Pijn *et al.*, 1991; Casdagli C *et al.*, 1997; Lehnertz, 1999; Elger *et al.*, 2000; Andrzejak *et al.*, 2001, 2006, 2011, 2012; Rummel *et al.*, 2011; Wang *et al.*, 2014; Bartolomei *et al.*, 2017).

## **8. Pre-processing, parameters for connectivity analysis**

In connectivity analyses, some parameters need to be tuned by the user, principally the size of the time windows, the step of the sliding-windows, and the maximum lags. These parameters could impact the results of connectivity obtained (Wang *et al.*, 2014; Fraschini *et al.*, 2016) and should be chosen adequately based on simulation study (Wang *et al.*, 2014) and adapted to the timing of neurophysiological processes that are investigated (Chu *et al.*, 2015). The choice of reference / montage is also crucial (Anastasiadou *et al.*, 2019), and it is recommended to use bipolar montage in order to limit effects of common source that increases the risk of spurious interdependence (Bartolomei *et al.*, 1999; Bastos and Schoffelen, 2016).

The duration of the analysed sample could also influence the connectivity results. Any statistical measure inherently yields only imperfect estimates of the desired quantity when calculated over a finite data window leading to the appearance of random correlations (Müller *et al.*, 2008). The non-stationary nature of the EEG signals is another potential concern and questions how long the analysed sample should be in order to extract robust functional connectivity. It has been shown that, although functional networks are highly variable on the order of seconds, stable network templates emerge after about 100 s of recording of resting-state (Kramer *et al.*, 2011; Chu *et al.*, 2012). Moreover a study compared 2, 5, and 10-minute data segments within a period of resting-state and observed similar connectivity results (Goodale *et al.*, 2019). Simulation study have confirm this finding suggesting sufficient duration being above 60s for iEEG (Wang *et al.*, 2014). However, by averaging connectivity estimation, one necessary loses the information about fluctuation of connectivity across time that could be potentially differ across studied zones. Further studies on this topic, notably using functional connectivity dynamics (Kopell *et al.*, 2014; Hansen *et al.*, 2015) on longer recordings, could be interesting.

The power spectrum of the signals has a major influence on the connectivity results in broad band. Hence, for any finite T, the width of the distribution, and therefore the probability for the occurrence of large correlation coefficients, gets larger with increasing power of low frequencies relative to fast components (Müller *et al.*, 2008). For example, in our study (Lagarde *et al.*, 2018), the  $h^2$  value was strongly influenced by the frequency contents, with lower frequencies having the greater connectivity strength. Therefore, in case a broadband functional connectivity analysis is used, the similarity of frequency contents of signals should be checked. If this content differs too significantly between regions, sub-bands analyses could be useful. Another, more complex and computationally costly method is the used of surrogate data (Schreiber and Schmitz, 2000; Stam, 2005; Kramer *et al.*, 2009; Rummel *et al.*, 2015). Surrogates testing have proved their usefulness in electrophysiological functional connectivity (Stam *et al.*, 2003; Müller *et al.*, 2008) with the combination of cross-correlation with surrogates to extract the “genuine cross-correlation” outperforming raw cross-correlation for both linear and non-linear methods (Rummel *et al.*, 2010; Andrzejak *et al.*, 2011). However, in our experience the estimated functional connectivity was far higher than surrogates functional connectivity, discarding potential spurious connectivity artefact (Lagarde *et al.*, 2018).

Electrophysiological signals, like many physical processes, have an amplitude inversely proportional to frequency (Bénar *et al.*, 2019). This means that considering the original (broadband) signal will be mostly influenced by the low frequencies. One way to cope with that is to ‘whiten’ the signals (Roehri *et al.*, 2016). Another more classical option is to filter the signals in difference frequency bands. This allows emphasizing different components of the signal, for example the actual ‘spiky’ part of the interictal discharges in contrast to the slow wave (Courstens *et al.*, 2016). In terms of interpretation, it is very important to

acknowledge that transient signal such as a sharp epileptic spike have energy spreading across many different frequency bands. Thus, filtering in a given frequency band does not guaranteed to observe actual oscillations within that band, but rather a mixture of actual oscillation, filtered transients as well as harmonics (Bénar *et al.*, 2010).

## **9. Spatial sampling, distance, volume conduction and reference effects**

The distance between recorded channels influences their estimated connectivity. Variations in the connectivity strength may be influenced by distances between sampled regions (Perinelli *et al.*, 2019). iEEG studies demonstrated a significant decrease of functional connectivity with increase in distance (Warren *et al.*, 2010; Lagarde *et al.*, 2018; Goodale *et al.*, 2019). Therefore, inter-region distance should be taken into account in order to perform adapted multivariate statistical analyses (Ridley *et al.*, 2017; Lagarde *et al.*, 2018) or to normalise the connectivity values using the decay of connectivity with distance observed in non-epileptic areas.

Most connectivity measures are affected by common sources in the signals that are compared. For example, use of a common reference or the fact that the same source can impact several sensors (“volume conduction” effects). The use of a bipolar montage (consecutive contacts, avoiding common electrodes in two channel pairs) can cancel reference effects and decrease volume conduction effects (Gotman and Levtova, 1996). Both volume conduction and reference effects lead to instantaneous (zero-lag) correlation between signals. Thus, methods have been developed to specifically remove such effects

(imaginary coherence (Nolte *et al.*, 2004), PLI (Stam *et al.*, 2007), phase slope index (Nolte *et al.*, 2008)), at the risk of lowering sensitivity to true connectivity at a small lags.

An intrinsic problem concerning iEEG studies is the necessary limited spatial sampling. Indeed, missing data (non-sampled regions) affects the results of network analysis and the difference in the spatial sampling across patients restricts the comparability across them especially for the graph-theory metrics. This issue could be in part overcome using surrogate data or permutation/resampling techniques (Conrad *et al.*, 2019). Moreover, the analysis at the level of region-of-interest (ROI) and not at the contact level probably helps to reduce the variability in the connectivity results obtained from various sampling (Bernabei *et al.*, 2021). Notably the reliability of graph-theory metrics depends on the number of implanted electrodes, and all metrics are not similarly sensitive to incomplete sampling: node strength, eigenvector centrality, and clustering coefficient, have the best performance compared to betweenness centrality. Therefore, the choice of the graph-theory metrics used is not trivial as each one shows specific methodological issues. Actually, computed quantities are more or less sensitive to the spatial sampling bias (Conrad *et al.*, 2019), fluctuate more or less during time (Geier and Lehnertz, 2017), and seem more or less correlated to epileptogenicity (Coito *et al.*, 2019).

## **10. Interictal epileptiform discharges**

A last potential confounding bias could be the presence of interictal epileptiform discharges (IEDs) and their intrinsic effect on the connectivity estimation. Studies found a correlation between higher IEDs frequency and higher connectivity values, however the effect was

limited (increase of about 5%) (Bettus *et al.*, 2008; Bartolomei *et al.*, 2013). Moreover, the suppression of periods with IEDs in connectivity analysis did not change the overall results on functional connectivity (Bettus *et al.*, 2008) or network topology (Bartolomei *et al.*, 2013). Simulation study have reported a small effect on connectivity strength and network structure (Hu *et al.*, 2019). Similarly (Park and Madsen, 2018) found relatively low overlap between the spiking zone and the zone with high granger causality values. Therefore, it seems possible to not necessary remove periods of IEDs for connectivity analysis. In addition, IEDs are intrinsic characteristics of the epileptogenic signal, and it should be inappropriate to remove them from the analysis. Moreover, the analysis of functional connectivity during IEDs may carry interesting information about the organisation of epileptogenic networks (Malinowska *et al.*, 2014; Coito *et al.*, 2015, 2016, 2019; Karunakaran *et al.*, 2017; van Mierlo *et al.*, 2019).

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