Defining epileptogenic networks: Contribution of SEEG and signal analysis

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CRITICAL REVIEW AND INVITED COMMENTARY

Defining epileptogenic networks: Contribution of SEEG and signal analysis

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Summary

Epileptogenic networks are defined by the brain regions involved in the production and propagation of epileptic activities. In this review we describe the historical, methodologic, and conceptual bases of this model in the analysis of electrophysiologic intracerebral recordings. In the context of epilepsy surgery, the determination of cerebral regions producing seizures (i.e., the "epileptogenic zone") is a crucial objective. In contrast with a traditional focal vision of focal drug-resistant epilepsies, the concept of epileptogenic networks has been progressively introduced as a model better able to describe the complexity of seizure dynamics and realistically describe the distribution of epileptogenic anomalies in the brain. The concept of epileptogenic networks is historically linked to the development of the stereoelectroencephalography (SEEG) method and subsequent introduction of means of quantifying the recorded signals. Seizures, and preictal and interictal discharges produce clear patterns on SEEG. These patterns can be analyzed utilizing signal analysis methods that quantify high-frequency oscillations or changes in functional connectivity. Dramatic changes in SEEG brain connectivity can be described during seizure genesis and propagation within cortical and subcortical regions, associated with the production of different patterns of seizure semiology. The interictal state is characterized by networks generating abnormal activities (interictal spikes) and also by modified functional properties. The introduction of novel approaches to large-scale modeling of these networks offers new methods in the goal of better predicting the effects of epilepsy surgery. The epileptogenic network concept is a key factor in identifying the anatomic distribution of the epileptogenic process, which is particularly important in the context of epilepsy surgery.

KEY WORDS: Stereoelectroencephalography, Signal processing, Brain networks, Focal epilepsies, Functional connectivity.

The brain is a complex network, evidenced by a plethora of neuroanatomic and neurophysiologic data ranging from microscale (at the neuron level) to macroscale (at the level of brain areas) studies. In this context, the idea that "focal" epilepsies are not in fact so focal, and involve networks of varying scales, has become progressively accepted in epileptology,[1–6] although this idea did raise some early criticism.[7] The network concept has been proposed as a key factor in identifying the anatomic distribution of the epileptogenic process, which is particularly important in the context of epilepsy surgery. It also offers a framework to describe the dynamic course of seizures and their clinical expression. However, with increasing use in an

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Key Points

- The concept of epileptogenic networks is historically linked to the development of the stereoelectroencephalography (SEEG) method
- A hierarchical organization of epileptogenic networks has been proposed in focal epilepsies
- Seizures in humans are associated with abnormal synchronization of distant structures as indicated by functional connectivity measures
- Ictal symptoms are related to the abnormal activation or to the disruption of network mechanisms governing normal brain function

epileptologic context, the meaning of "network" needs to be clarified. In contrast with other brain diseases, epilepsies are heterogeneous and involve unstable brain states (interictal vs. ictal). The definition of epileptic networks is also largely dependent on methodologic approaches. Epilepsies are characterized by altered brain rhythms; consequently, the study of electrophysiologic changes is crucial.

In this context, intracerebral electroencephalography (EEG) offers a unique means of exploring the pathophysiologic process, allowing high-resolution mapping of biomarkers of epileptogenicity.[8] This approach is complementary to neuroimaging studies (for reviews Laufs,[3] Guye et al.,[4] and Pittau et al.[9]), which aim at investigating structural and connectivity changes. Structural neuroimaging may demonstrate extension of cortical abnormalities outside the epileptogenic zone (EZ) as measured by cortical thickness or volumetry (review in Bernhardt et al.[10]). Diffusion tensor imaging (DTI) tractography may show alterations in the microstructure of brain tracts, and functional magnetic resonance imaging (fMRI) studies show connectivity changes in the regions affected by seizure activity.[3,4,9] The relationship between these changes and electrophysiologic markers is still, however, poorly understood, especially due to the scarcity of studies comparing intracerebral EEG and MRI/fMRI data.[11]

In this review, we discuss the rationale for the concept of epileptogenic networks, focusing particularly on several studies from our group using stereo-electroencephalography (SEEG) signal analysis.

Historical Considerations and SEEG Recordings of Seizure Onset

Depth EEG recording in epilepsy presurgical assessment originates from the need to better define brain regions involved in genesis of an individual's epileptic seizures. Such definition is necessary to design an optimal surgical strategy, that is, which aims to render the patient seizure-free while avoiding unacceptable postoperative deficits. The SEEG method was developed in the 1960s by Talairach and Bancaud[12] and consists of stereotactic implantation of multiple intracerebral electrodes targeting different brain areas. This allows for recording in multiple distributed sites, including in certain cases subcortical regions. Especially over the last decade, the SEEG method has become increasingly widely used internationally[13] (Fig. 1A). This recent trend toward wider use of SEEG likely reflects evolution in indications for epilepsy surgery evaluation, with extratemporal and nonlesional MRI-negative cases increasingly observed in different epilepsy surgical centers around the world.[14] It should be emphasized that the SEEG method, by definition, leads to placement of intracerebral electrodes in structures the possible involvement of which in seizure onset and/or propagation is hypothesized based on all available noninvasive data for a given patient. Typically, 8–15 electrodes are implanted (generally 0.8 mm diameter, with multiple contacts 2 mm long and 1.5 mm apart), allowing simultaneous recording from multiple sites including mesial and lateral regions. Of course, the value of the electrophysiologic data obtained in each case, and whether the seizure organization is adequately identified, depends on the accuracy of the initial hypotheses, and precision of electrode placement. The spatial sampling of the epileptogenic network is an important issue in SEEG. The number of electrodes and the selection of sampled regions in each patient is necessarily restricted, which may constitute a limitation in comparison with more global brain network approaches (using MRI or magnetoencephalography [MEG], for example).

An early observation from Bancaud and Talairach's SEEG studies was that the electrical disturbances arising from the presence of an epileptogenic cerebral lesion did not respect anatomic boundaries. In addition, seizures could be observed to arise from structures quite distant from the lesion and even separate from the region of maximal interictal spiking.[15] Fundamental to the original concept of the EZ was the idea of a set of interrelated brain regions involved in the primary organization of the ictal discharge, rather than a focus. The conceptual difference between this original formulation of the EZ arising from observations based on SEEG, and subsequent definitions of the EZ based largely on subdural grid use in presurgical evaluation, has been highlighted previously.[16] The idea of "epileptogenic networks" subsequently stemmed from these early observations and is fundamentally related to the SEEG recording method.[17] Indeed, well ahead of their time, Bancaud and Talairach effectively paved the way to the concept of epileptogenic networks, a fact readily forgotten in the current era of functional neuroimaging and signal analysis. This view arose because the SEEG, for the first time, allowed simultaneous recording from multiple cortical and subcortical structures, which were seen to be concurrently involved in seizure organization, and whose anatomic relation could be precisely defined (Fig. 1B,C). With regard to the organization of the EZ, two schematically different

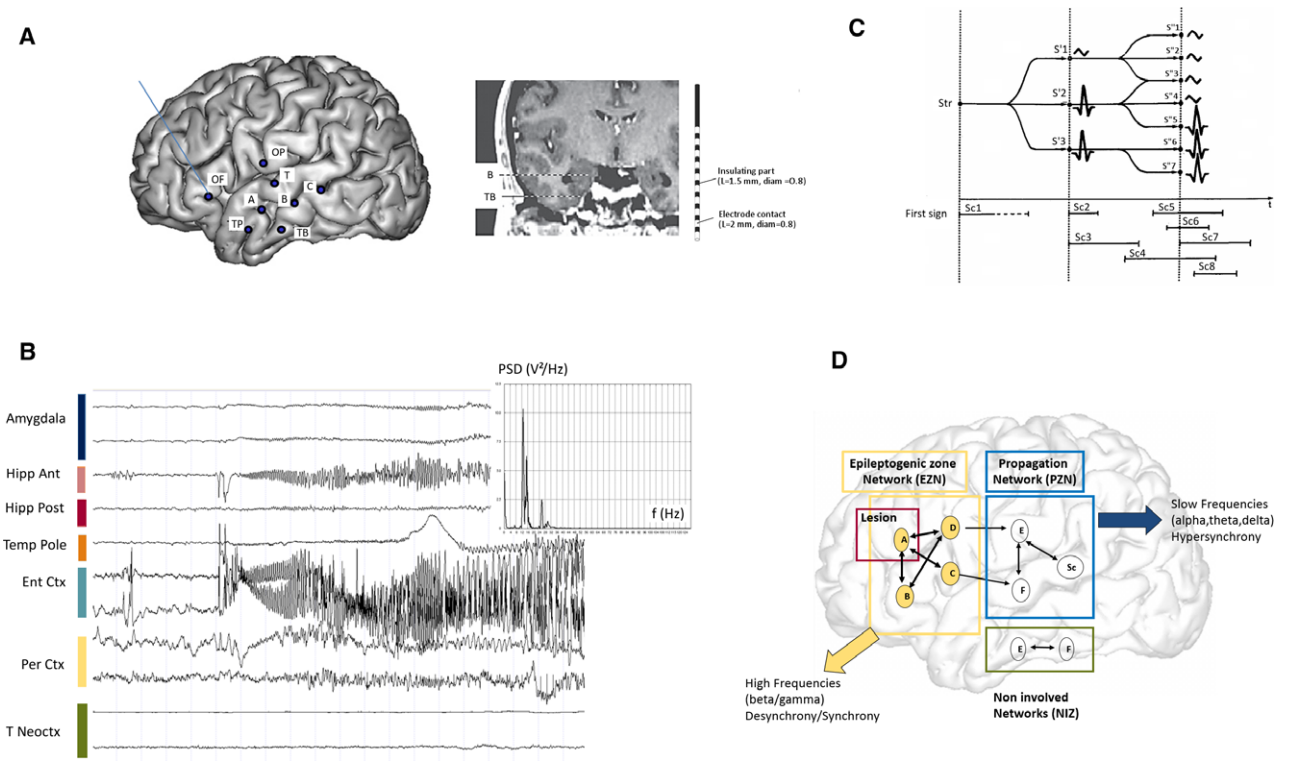

Figure 1.

(**A**) Schematic diagram of the electrodes used in SEEG exploration (L = length, diam = diameter) in a case of temporal lobe epilepsy, along with reconstruction of the trajectory of the electrodes Tb and B superimposed on the coronal MRI view. (**B**) SEEG recordings of ictal activity in a case of temporal lobe seizure. Seizure starts from different regions of the mesial temporal lobe: a rapid discharge affects contacts from amygdala (internal contacts electrode A), hippocampus (anterior hippocampus (Hipp Ant) internal contacts electrodes B and posterior Hipp Post C), and from entorhinal cortex (Ent Ctx, electrode TB internal contacts). The power spectral density (PSD) is shown, measured from the entorhinal cortex rapid discharge and disclosing a fundamental frequency at 15 Hz. (**C**) Schematic representation of the correlation between changes in SEEG activity and the appearance of clinical signs from Bancaud and Talairach[97]. This is one of the earliest view of the network concept. The appearance of clinical signs (SC1, SC2, etc.) is associated with the temporal involvement of different brain regions (S′1, S′2, etc.), following an "in series or in parallel" configuration. (**D**) The concept of epileptogenic networks in focal epilepsies is illustrated. The cerebral regions are represented by letters (A, B, etc). The scheme proposes a hierarchical organization in terms of epileptogenicity in the epileptic brain. The EZ includes different brain regions that are able to generate seizures, in particular, fast activities, defining the EZ Network (labeled A, B, C, and D). A represents a region with putative (visible or not) lesion. The EZ Network is also characterized by a pattern of synchrony–desynchrony. A second set of regions are less epileptogenic, are triggered in seizures by the EZ, and are within the "propagation zone network" (E, F, SC, and H). SC schematizes the involvement of subcortical (thalamus for instance) regions. Activity recorded in these regions is generally of lower frequency and more synchronized than in the EZ. Some regions are not involved during seizure propagation (NIN, noninvolved network, G, H).

situations may be observed. In some cases, the EZ corresponds to a relatively restricted area of the brain, in which seizure onset is limited to a unique dysfunctional area, a situation corresponding to the classical notion of an epileptogenic focus (see Rosenow and Luders[16]). However, in many cases the seizure onset is characterized by discharges that simultaneously or very rapidly involve several distributed brain regions.[2,12,18] In this situation, the model of the epileptogenic focus cannot accurately describe the spatial organization of the EZ. Figure 1A shows one example of distributed areas generating seizures in a case of temporal lobe epilepsy (TLE). In this example, the seizure appears to start simultaneously from at least three distinct regions of the temporal lobe. Secondary delayed electrophysiologic discharges are observed in regions outside the EZ and are consistent with the concept of propagation. However, the propagation of seizures is a complex process that does not correspond to the classical propagation of the nerve flux. Indeed, long delays may occur from one region to the other, probably linked to gradual changes in the biologic properties of the involved regions.[19,20] The anatomic sites involved during seizures depends on the structural connectivity[21]; both cortical and subcortical structures are involved.[22] Thus propagation is determined by local as well

as connectivity properties rather than passive conduction. In terms of epileptogenicity, a hierarchical organization of epileptogenic networks has been proposed in focal epilepsies describing brain regions involved in seizure genesis and propagation, as summarized in Figure 1D.

Methods for Recording and Analyzing Epileptogenic Networks

The simplest and most direct approach for investigating epileptic networks is based on mapping the level of activation of individual functional units (neurons, and small or large brain areas).[23] In human epilepsy, the recording of different brain areas with depth electrodes or the analysis of local changes of cerebral blood flow during seizures are examples of such studies. The observation that a set of distributed regions can be involved during seizures or during interictal events (as studied, for example, by simultaneous EEG-fMRI) is a first argument for the application of network theory in focal epilepsies.[24,25] More specific approaches are based on the quantification of the seizure-onset zone using frequency or time–frequency analysis of intracerebrally recorded signal[26] including in particular the epileptogenicity index (EI)[27] and epileptogenicity maps (EMs).[28] The value and precision of all these approaches clearly depend on spatial (SEEG) and temporal (fMRI) sampling issues. In particular, SEEG electrodes must be optimally placed if meaningful data are to be obtained.

Connectivity analysis

A second approach is based on functional connectivity (Fc) approaches, which describe brain function through mathematical estimates of the links between two signals (originating from different brain regions), reflecting how different brain areas coordinate their activities.[29–31] This approach can use signals from different sources (EEG, SEEG, and blood oxygen level–dependent [BOLD] signals) and may focus on the ictal or on the interictal state. Of particular interest in epileptology, noninvasive studies of Fc using EEG or MEG signals can be performed at the channel level or using source reconstruction[32–35] or independent component analysis.[36] Other noninvasive Fc approaches using BOLD signals have also been used extensively showing complex changes that are not always concordant with electrophysiologic changes.[11,37,38] Nevertheless, although underlying mechanisms of Fc changes are still not fully understood, there is a growing amount of data showing the potential usefulness of these methods.[39,40]

Using SEEG signal analysis, numerous methods have been proposed for measuring linear (coherence, linear regression analysis) or nonlinear (mutual information, nonlinear regression analysis, similarity indexes based on state-space trajectories reconstructed from observed signals) properties of the relationship.[41] Correlation between time series can be estimated directly on the time series[42] or in the frequency domain.[43] More recently, it was proposed that the correlation coefficients could be computed in the wavelet domain, where time resolution can be adapted as a function of frequency.[44] It has been shown that in different models of epileptic processes, the results of each method strongly depend on the underlying coupling model between time series.[41,45] In one study,[41] regression analysis offered a good compromise (with good or average performances) for detecting coupling changes. Nonlinear regression analysis was found to be particularly efficient for estimating functional connectivity from signals simulated from coupled neuronal populations (the so-called physiologically grounded "neural mass" models). Nonlinear regression analysis provides a metric, referred to as the nonlinear correlation coefficient h^2, which takes values in the interval [0, 1].[46–48] Low values of h^2 denote that two signals, X and Y, are uncorrelated (in the nonlinear sense). High values of $h^2_{X\to Y}$ mean that the second signal Y may be explained by a transformation (possibly nonlinear) of the first signal X.

Causality analysis

Several methods have been proposed to estimate the direction of coupling and thus to identify network leaders, often referred to as "causality" analysis. One definition of causality has been formulated by Granger in econometrics,[49] whereby a time series x(t) is considered to cause another series y(t) if knowledge of the past values of x(t) improves the prediction of y(t) compared to past values of y(t) alone. One of the first applications in electrophysiology involved a study in awake monkeys, showing that synchronized beta oscillations could bind in multiple sensorimotor areas during a motor maintenance task.[50] Extensions of Granger causality to multichannel EEG/MEG data have been proposed. The "directed transfer function" (DTF)[51] has been used in epilepsy.[52,53] DTF estimates relations, not only along direct pathways, but also along indirect pathways. To overcome this problem, which can hamper correct characterization of networks, "direct DTF" (dDTF) emphasizes direct associations over indirect ones.[54] Another algorithm implementing the concept of Granger causality in the frequency domain is partial directed coherence (PDC[55]). PDC was recently applied to the localization of the epileptogenic zone.[56] However, all these methods are based on linear assumptions for the relationship between signals estimated by multivariate autoregressive (MVAR) models. It is also possible to estimate directed connectivity based on nonlinear measures, in particular non-linear regression. Wendling et al.[47] proposed estimation of a direction index "D" from the nonlinear regression measure. This index considers both the estimated time delay between signals X and Y (latency) and the asymmetry property of the nonlinear correlation coefficient h^2 (as values of the h^2 coefficient are different if the computation is performed from X to Y or from Y to

X). Values of D range from −1.0 (X is driven by Y) to 1.0 (Y is driven by X).

Graph theory–based analysis

A third level of approach is based on "graph theory," which allows (generally based on pair-wise interactions) the description of both global and local characteristics of the networks.

In the global approach, characteristics such as clustering, path length, and modularity are estimated from connectivity graphs.[23] A complex dynamical network can be mathematically described as graphs with a set of n nodes associated by k connections or edges.[23,57] Such a representation allows the definition of parameters quantifying network characteristics. Thus not only their connection topology but also their potential behaviors may be extracted. The most popular model is the "small world," introduced some years ago by Watts and Strogatz.[58] Small-world networks correspond to an intermediate state between a regular network (i.e., all nodes are related only to their nearest neighbors) and a random network (i.e., all nodes are related randomly). A small-world network is considered an efficient network architecture, balancing both network integration and segregation processes, which characterize normal human brain function. This mathematical model is based on the evaluation of two parameters: the clustering coefficient C and the characteristic path length L. The clustering coefficient C, which is the likelihood that neighbors of a vertex will also be connected, is a measure for the tendency of network elements to form local clusters. The characteristic path length L is the average of the shortest distance between every pair of vertices counted as a number of edges. The characteristic path length L indicates how well network elements are integrated or interconnected.[58] In focal epilepsy and from intracerebral EEG signals, these parameters can be estimated in the preictal period,[59] during ictal activity,[60,61] or in the interictal state.[62]

In the local approach, parameters are calculated at each node, in particular to estimate "hubs" in the networks. The degree parameter represents the number of connections linking each node to other nodes. "In degrees"/"out degrees" represent the number of incoming/outgoing links, respectively, from any given node, and total degree is the sum of in and out. A variant that does not rely on thresholding is node strength, where the connectivity values are summed at each node. Several studies have proposed using either degrees or strength for characterizing the most important nodes within the epileptic network, either in the interictal, the preictal, or the ictal period.[63–65] The centrality of a given node can be defined as the number of shortest paths between any two nodes that pass through this node.[31] Betweenness centrality is the sum of the ratios between the number of shortest paths (between sites i and j) that pass through a given node n, and the total number of such paths between i and j (for review see Guye et al. [31]). Another approach called Local Information has also been introduced[66] aiming at measuring the amount of information passing through a given node. The most immediate advantage of graph theory is to provide a way to summarize potentially very complex graphs of interactions. For example, the degree measure allows attribution of one figure per node that assesses its importance in the network, in a way that is easy to interpret. Other measures in particular, global measures, can more difficult to interpret in an intuitive way, even though they are potentially important biomarkers of brain function and dysfunction. Although graph approaches have gained in popularity over the past 10 years, the neurobiologic basis of these concept is not obvious. The interpretation of measures taken from graph theory in terms of clear neurophysiologic concepts is still a subject of debate.[67]

The Epileptogenic Zone Network: Brain Networks Involved in Seizure Generation

Analysis of SEEG changes at seizure onset

Seizure onset is characterized by dramatic changes in brain rhythms. Several patterns of onset may be observed during SEEG recordings,[68,69] most commonly low voltage fast discharge-(LFD). The LFD may be preceded by EEG changes in the form of preictal epileptic spikes, train of spikes or slow-wave complexes.[68] Frequencies involved in the LFD range from beta/low gamma (15–30 Hz; e.g., in mesial temporal seizures) to higher frequencies (gamma range, 30–100 hz, generally observed in neocortical seizures).[27,70] As indicated above, the seizure onset characterized by LFD involves often distant and functionally distinct brain sites almost simultaneously. This has been confirmed by quantification of LFD using computational/mathematical measures.[26–28,71] The largest evidence comes from the use of the epileptogenicity index (EI) method. From SEEG signals, the EI combines analysis of both spectral and temporal features, respectively, related to the propensity of a brain area to generate fast discharges (12.4–97 Hz), and to the earliness of involvement of this area in the seizure.[27] Results may be shown in a three-dimensional (3D) representation of the patient's MRI[72] (Fig. 2). Another approach has been proposed to quantify epileptogenicity from SEEG recordings by adopting a neuroimaging approach, in order to generate statistical parametric maps of high-frequency oscillations (HFOs) at seizure onset, called epileptogenicity maps (EM).[28] EI studies have shown that the EZ in drug-resistant epilepsies is generally formed by at least two distinct epileptogenic areas. For example, in TLE, the most complex networks are observed in mesiolateral or "temporal plus" (perisylvian) subtypes, where a large set of regions are epileptogenic.[73] Bitemporal epilepsies are characterized by an EZ that preferentially involves subcortical regions,[74] whereas larger networks have been observed in patients

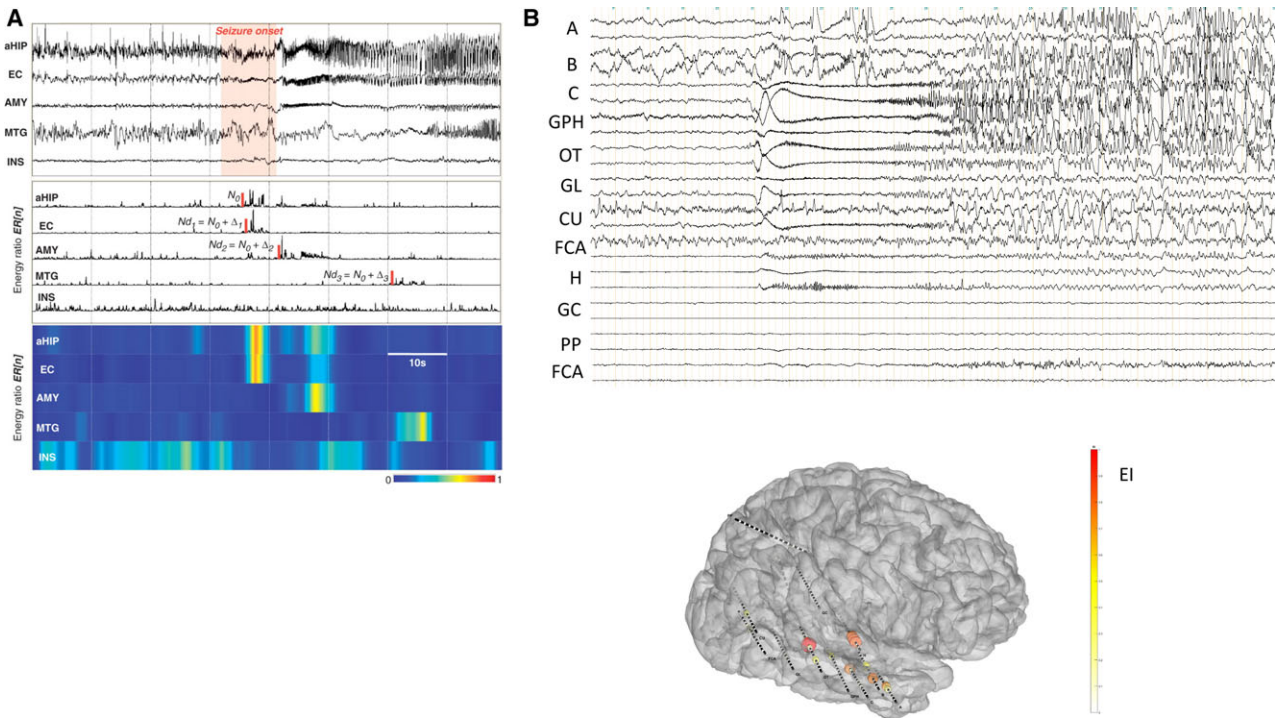

Figure 2.
(**A**) Epileptogenicity index assessment. The Page-Hinkley algorithm provides a detection time Nd1 (red marks) for each brain structure if involved in the generation of a rapid discharge. The first detection time is arbitrarily defined as the reference time N0 (aHIP in this case). Then, for each EEG signal recorded from a given brain structure (aHIP, anterior hippocampus; EC, entorhinal cortex; AMY, amygdala; MTG, middle temporal gyrus; INS, insula). The epileptogenicity index (EI) is defined as the energy ratio ER[n] (time interval following detection) divided by the delay Δi of involvement of the considered structure with respect to time N0. The color-coded map shows the evolution of the energy ratio with time (same information as that contained in b). From top to bottom, this representation displays the early involvement of the anterior hippocampus (aHIP) and the entorhinal cortex (EC) as well as the delayed rapid discharge in the amygdala (AMY) and then in the middle temporal gyrus (MTG).[27] (**B**) SEEG recordings of an "occipital plus" seizure and representation of the epileptogenicity index (EI) values on the electrodes contacts projected into the individual MRI. EI values were computed on a bipolar montage, and they are drawn between each pair of contacts of the bipolar derivation. The diameter and position on the color scale are proportional to the normalized EI values. Note that several regions appear to be epileptogenic and involved at seizure onset.[72]
Epilepsia © ILAE

with normal MRI versus hippocampal sclerosis in temporal lobe epilepsy.[27] This has been also found in parietal epilepsies,[75] frontal,[76] and occipital epilepsies,[72] where complex EZ networks are frequently observed. EMs have been used to quantify the EZ in patients with startle seizures and elegantly showed the involvement of the supplementary motor area.[77] Surgical prognosis has been found to correlate with the number of epileptogenic regions in TLEs.[27,73]

In the context of surgery, the role of the epileptogenic lesions in the network of regions generating seizures is a crucial issue. A study dealing with the estimation of epileptogenicity of focal cortical dysplasia and sites remote from the lesion found that high epileptogenicity values could be found in remote sites in 60% of patients and that surgical outcome was better in patients with a focal pattern.[78] In epilepsy related to cavernomas, an EZ network largely extending outside the limits of the lesion was observed in the majority of cases.[79] These approaches have also added information about the possible evolution of the network size with time. A positive correlation between the duration of epilepsies and the number of epileptogenic regions (defined by a high EI value) has been found in temporal lobe epilepsies[27] and in frontal epilepsies.[76] These results advocate for a secondary epileptogenesis process in human focal epilepsies at least in some anatomic localizations and some etiologies of the epileptic process.

Changes in functional connectivity during focal seizures

It has long been known that epileptic phenomena are associated with changes in brain synchrony.[80] Seizures in humans are associated with the abnormal synchronization of distant structures as indicated by functional connectivity measures.[22,60,81–86] Although seizure onset is often marked by a dramatic decrease of synchrony among recorded brain structures,[85,87] the largest changes in terms of increased network synchrony are observed during seizure spread and

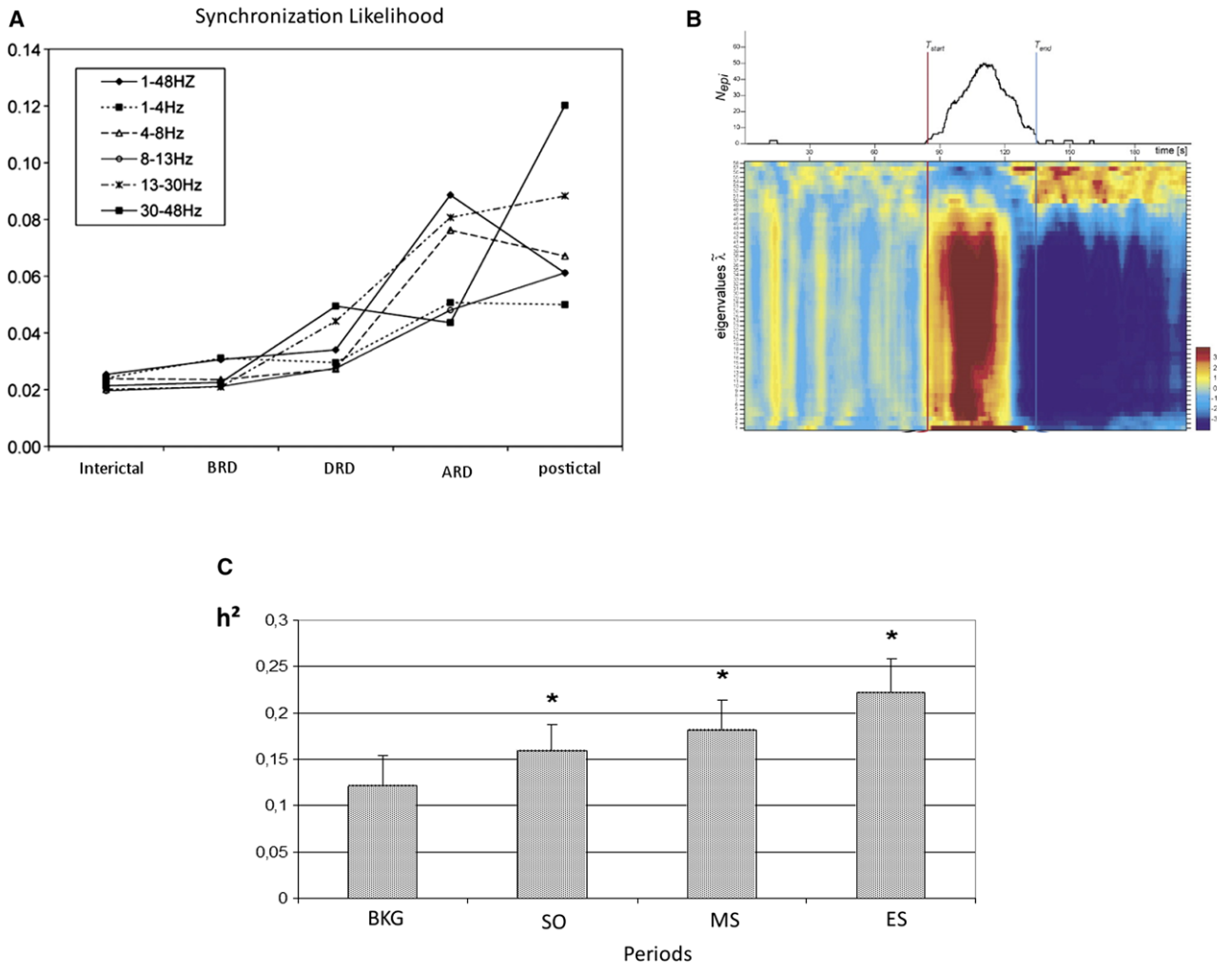

Figure 3.

Examples of studies showing by three different methods the global changes observed in Fc during the course of focal seizures. (**A**) This picture shows, in the different EEG sub-bands, the increased synchrony (average values) from the beginning to the end of mesial temporal lobe seizure. Fc is estimated using the synchronization likelihood (SL) method.[60] (**B**) A:Correlation analysis of complex partial seizure.[84] The number of EEG channels recording epileptiform activity $N_{epi}(t)$ is plotted from seizure onset T_{start} to seizure ending T_{end}. B. Spectrum of the correlation matrix of a sliding window w are displayed smoothed by a moving average of 5 s duration. Each column corresponds to the spectrum of the correlation matrix computed when w reached this position in time (normalized eigenvalues $\lambda i(t)$). An increase in the eigenvalues reflecting an increase of EEG correlation beginning before the seizure terminates. (**C**) Increased correlations are observed between SEEG signals from mesial temporal regions, neocortical temporal regions, and thalamus, from the interictal period to the end of the seizure. Fc is estimated using nonlinear regression, and the level of correlation is given by the average h^2 values from all the pair-wise interactions. BKG, interictal period; SO, seizure onset; MS, middle part of seizures; ES, end of seizures.[22]

termination[22,60,84,88–90] (Fig. 3). These changes in the "propagation network" are probably largely responsible for the emergence of clinical symptoms (see section Network changes and clinical seizure expression).

Some studies have focused on the seizure-onset period and the transition from the interictal to ictal period. This onset involves often distinct brain sites, and it has been hypothesized that a synchronizing phenomenon is involved at the simultaneous start of fast oscillations.[91] The spatiotemporal dynamics of these phenomena have been investigated using functional connectivity measures at seizure onset, particularly in temporal lobe seizures (TLS).[18,46,64,83,92,93] Signal quantification methods have demonstrated preferential functional links that may serve as a basis for a classification of involved network. Subtypes of TLS according to the interactions between mesial (amygdala–hippocampus–entorhinal cortex) and neocortical structures have been proposed: mesial, mesial-lateral, and lateral-mesial, and lateral.[46,83] In the most prevalent mesial group, functional coupling between several regions

belonging to the mesial structures is frequently observed, as well as absence of coupling between mesial and neocortical structures at seizure onset.

The correlation between SEEG signals tends to be maximal before the emergence of the LFD (during the immediate preictal period) and to decrease just after, followed by later increase during the seizure course (Fig. 4A). Preictal synchronization has been quantified in a group of patients with mesial temporal lobe epilepsy (MTLE), by studying the interactions between entorhinal cortex, hippocampus, and amygdala.[92] Most of the interactions were prominent between the entorhinal cortex and the hippocampus. Analysis of coupling directionality indicated that most of the couplings were driven either by the hippocampus or by the entorhinal cortex (four patients). The rapid discharge period was characterized by a significant decrease of cross-correlation values. This approach has been recently extended to other types of epilepsies, with larger numbers of nodes considered in the network analysis.[65] This work used graph measures of IN and OUT strength and revealed that the out strength and total strength measures of nodes in the preictal period matched the seizure-onset zone as defined by the epileptogenicity index (Fig. 4B). These findings are consistent with the study by van Mierlo et al.[64] which were obtained on mixed electrocorticography (ECoG)/intracerebral recordings with a different connectivity method and visual analysis of the epileptogenic zone. Another recent study has evaluated graph analysis based on directed coherence measures in SEEG recordings of focal cortical dysplasia (FCD).[86] Authors showed that nodes within the lesion play a leading role in generating and propagating ictal EEG activity (Fig. 4C). The desynchronization between signals observed after a first phase of synchrony was also found to be particularly important in signals from neocortical sites in neocortical seizures associated with gamma activities.[87] Finally, the pattern of synchronization/desynchronization between regions

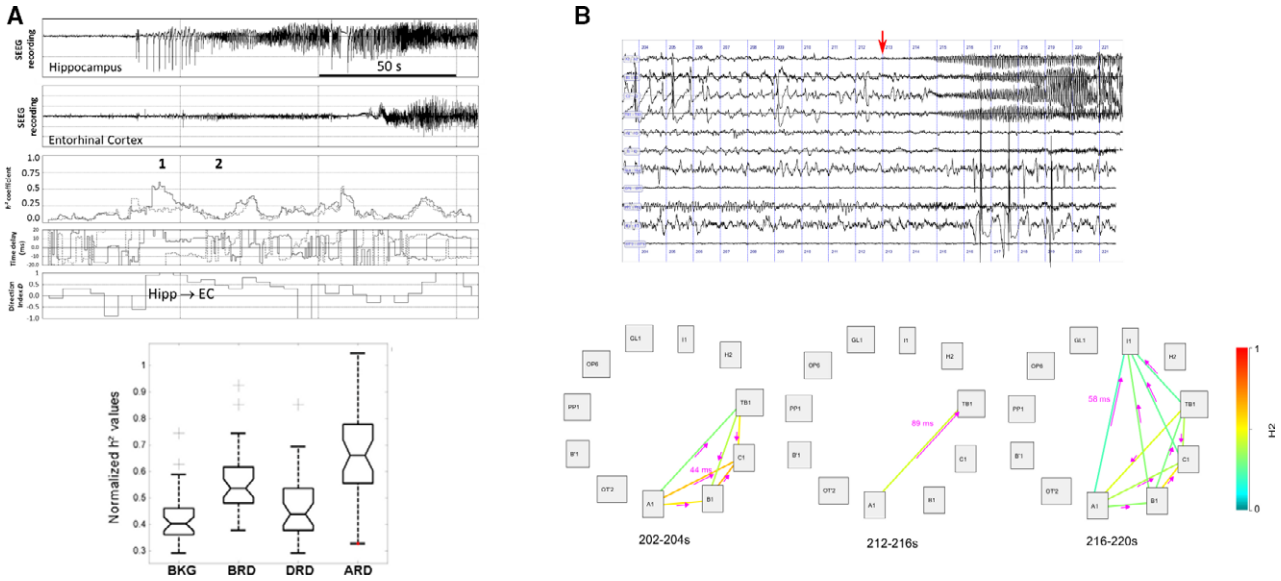

Figure 4.
The phenomenon of synchronization/desynchronization during focal (here, temporal lobe) seizures. (**A**) Upper part: functional coupling between entorhinal cortex and hippocampus in a patient with mesial temporal lobe seizures is studied using nonlinear regression (h^2). An increase of synchrony (1) during the phase of preictal spiking is observed as measured by the h^2 coefficient between the two structures. The direction index D indicates that the activity in the hippocampus is leading (positive values) the activity recorded in the entorhinal cortex. Note that the rapid discharge is associated with a decrease in correlation (indicated as 2 in the figure). Lower part: Box plot performed on normalized values of nonlinear correlations h^2 values averaged from interactions between entorhinal cortex, amygdala, and hippocampus in SEEG recorded mesial temporal lobe seizures. The values are obtained in the BKG (background, interictal), BRD (before rapid discharge), DRD (during rapid discharge), and ARD (after rapid discharge) periods. h^2 values measured before the rapid discharge (BRD) are significantly higher than those measured during background activity (BKG) and during the rapid discharge itself (DRD) (adapted from).[92] (**B**) Example of temporal lobe seizure (red arrow indicates the seizure start). Lower part: Examples of h^2 graphs corresponding to different time windows during the seizure. Each bipolar selected channels from SEEG is shown (GL1, I1, etc.). The delay between channels permits estimation of a direction for each link. In the graphs, the number of ingoing and outgoing links for each channel are counted. Note that the preictal synchrony between mesial regions is well visible before the decrease of correlation during the rapid discharge (from Courtens et al.[65] and Varotto et al.[86]).

forming the EZ appears to be a characteristic property of the EZ and may be observed in many different forms of partial seizures.

Propagation Networks: Involvement of Cortico-subcortical Loops

The propagation of seizures in the brain is associated with important changes in Fc. This has been studied particularly in TLS, where it has been shown that the thalamus (TH) plays an important role. The role of synchronized thalamocortical oscillations has been suggested in animal models of temporal lobe seizures[94] and has been proposed to act as a seizure amplifier and synchronizer. Thalamic involvement during SEEG-recorded TLS has been well described.[22] The synchronization between signals from temporal lobe structures and the thalamus has been investigated in human SEEG-recorded TLE.[22] The results demonstrated overall increased correlation between thalamus and temporal lobe structures during seizures, particularly neocortical/thalamus interactions (Fig. 5A,B). Correlation values at the end of the seizure were significantly higher than values at seizure onset ($p < 0.0001$), and thalamocortical synchronization was found to predominate at the end of seizures. Seizure termination has been proposed to be caused by a large increase in signal synchrony.[84] In addition, the extent of thalamocortical correlation during seizure course was found to correlate with the surgical outcome, suggesting that extension of the epileptogenic network to subcortical structures could hamper the efficacy of surgery.[22]

The role of thalamocortical synchronization in seizure termination has been more specifically investigated in a recent study.[90] The functional connectivity between thalamus and cortical regions was estimated using nonlinear regression analysis and a measure of IN and OUT degrees (Fig. 5C,D). Thalamic synchronization was significantly more elevated at the end of seizures than at the onset and negatively correlated with seizure duration ($p = 0.045$). Some seizures displayed a particular thalamocortical spike-and-wave pattern at the end. These seizures displayed a higher and sustained increase of cortical and thalamocortical synchronization with a stronger participation of thalamic outputs. In this subgroup of seizures, the thalamus could exert an important control on temporal lobe structures by inducing stable hypersynchronization that ultimately leads to seizure termination.

Global topologic changes have been described during intracerebrally recorded seizures, showing a tendency for a shift toward a more ordered network during seizure development. Ponten and coworkers showed that increasingly regular topology is a characteristic of seizure activity in temporal lobe seizures recorded with depth electrodes.[95] Very similar results were obtained by Kramer et al.[89] during partial seizures recorded from neocortical grids. Schindler et al.[96] also found an increase of C and L at seizure onset in their analysis of EEG recordings from 100 epilepsy patients. To date, however, the neurophysiologic interpretation of these changes are unclear, although they reflect profound changes in brain functional organization.

Network Changes and Clinical Seizure Expression

Anatomoclinical–electrical correlation is a process fundamental to the SEEG method, comparing electrical activity from different explored regions in real time as clinical expression of seizures emerges (Fig. 1C).[97] By definition, the first clinical signs are observed after electrical seizure onset (typically several seconds after) and are often largely related to propagation of the discharge. The study of clinical seizure signs with regard to EEG changes in functional connectivity offers new opportunities to better understand the underlying seizure architecture and cerebral substrate of semiologic production. In the healthy brain, cognitive and emotional processes are dependent on precise integration of neural activity at specific spatiotemporal scales.[23,98] Spontaneous seizures or seizures obtained after electrical stimulation can be studied in this context. During SEEG, electrical stimulations using low frequency (typically 1 Hz) or high frequency stimulations (typically 50 Hz during 5 s) are used to map functional cortex or to trigger seizures.

Ictal clinical symptoms could be related to the abnormal activation of physiologic neural networks by epileptic rhythms; or on the contrary, to the disruption of mechanisms governing normal brain function. The former situation can be seen in ictal symptoms that represent an elaborated form of normal phenomena. One example is the "dreamy state" (including "déjà vu-déjà vécu" sensations or reminiscence of visual memories), which is related to epileptic discharges involving the memory systems of the mesial temporal lobe. The dreamy state is more frequently observed after stimulation of the rhinal cortices than after stimulation of the hippocampus or the amygdala.[99] In one patient from this series (Fig. 6A), SEEG functional connectivity was estimated between signals generated at the time of the memory recollection induced by the stimulation. Transient theta range synchronization involving mesial temporal lobe structures as well as visual association cortex was observed during reminiscence.[100] "Déjà vu" is another example of the abnormal activation of a cerebral network during stimulation (and probably during seizures) leading to a clinical symptom. Functional connectivity between SEEG signals was studied in epileptic patients in whom "déjà vu" was induced by electrical stimulation:[101] stimulations triggering "déjà vu" were associated with increased EEG correlation in the theta band (Fig. 6B) between rhinal cortex, amygdala, and hippocampus. Another example is the humming/singing automatism

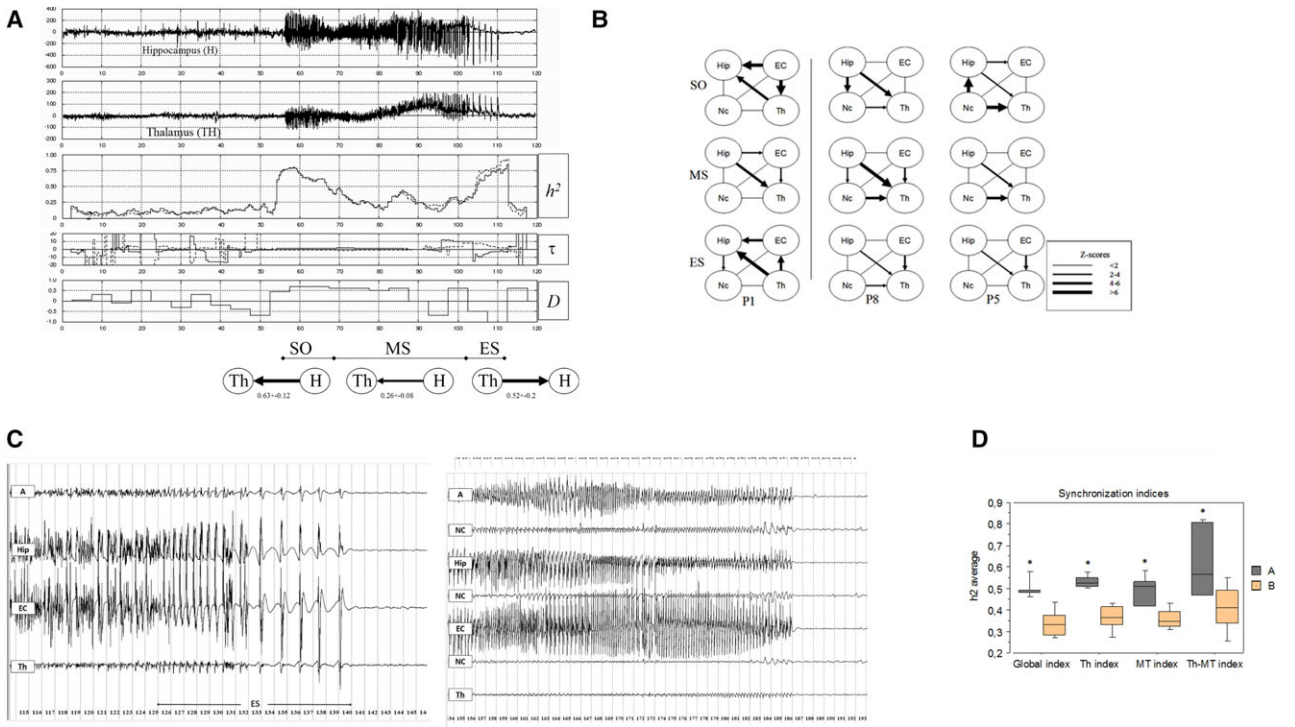

Figure 5.

(**A**) Interaction between thalamus (Th) and hippocampus (Hip) in a TLE seizure. On each pair of signals, nonlinear regression analysis is used to compute the nonlinear correlation coefficient h^2 (third panel) and the time delay τ from upper signal to lower signal (fourth panel). Asymmetry information (difference between h^2 coefficients) and time delays are jointly used to compute the direction index D that characterizes the direction of coupling (lower panel). (**c**) h^2 values are averaged over considered periods and information is represented as a graph. Line thickness is proportional to the average h^2 value, and the arrow indicates coupling direction, when significant. A large increase in correlation is observed in the first period, and the direction index D indicates that the mesial structure (hippocampus) is leader. The second period (MS) is characterized by the maintenance of a significant correlation, and the D index also indicates that H is leader. The last period is characterized by a re-increase of h^2 values. D index values are now negative, indicating that the thalamus (TH) is now the leader structure.[22] (**B**) Scenarios of thalamocortical and cortico-cortical couplings in three cases of MTLE with early involvement of the thalamus. The three ictal periods are represented (SO, seizure onset; MS, middle part of the seizure; ES, end of seizure). Coupling between structures is shown when significant increase is observed relative to the reference period (z-score >2). Direction of coupling is based on the direction index D estimated from nonlinear correlation.[22] (**C**) SEEG recordings of two MTLE seizures showing the end of seizures in one case displaying the thalamic rhythmic pattern with a spike-wave activity (pattern A, on the left) or another pattern of termination (pattern B, on the right). A, amygdala; Hip, hippocampus; EC, entorhinal cortex; NC, neocortex; Th, thalamus. (**D**). Pattern A seizures showed higher thalamic synchronization indices (Th index) and thalamic output measures (Th OUT) than pattern B seizures in the end of seizure period. That means that in these patterns, synchrony with the thalamus is higher, and effective connectivity is in favor of a leader role of the thalamus.[90]

sometimes observed in temporal lobe seizures. In three patients explored with SEEG, Fc analysis (characterized by the coherence averaged over the frequency band) disclosed a pattern of synchrony between the temporal superior gyrus and the prefrontal cortex during humming (Fig. 6C).[102] These examples suggest that ictal activity, by inducing functional changes in areas remote from the EZ, can trigger physiologic-range activity in neural networks involved in some specific brain functions such as memory and music.

Excessive synchrony has also been suggested as a mechanism contributing to loss of consciousness (LOC) in complex partial seizures, by interfering with the mechanisms of conscious access and representation.[103] Some models of conscious representation postulate the existence of a global workspace that processes conscious information via synchronized activity within widely distributed neuronal modules.[104] The relationship between neural synchronization and loss of consciousness in 12 patients with temporal lobe seizures was studied in patients undergoing SEEG,[88] showing that LOC during TLS is characterized by increased long-distance synchronization between structures that are critical in processing awareness, including thalamus and parietal cortices (Fig. 6D). In addition, the degree of LOC was correlated with degree of synchrony in thalamocortical systems along a nonlinear curve, suggesting a bistable system. This result has been

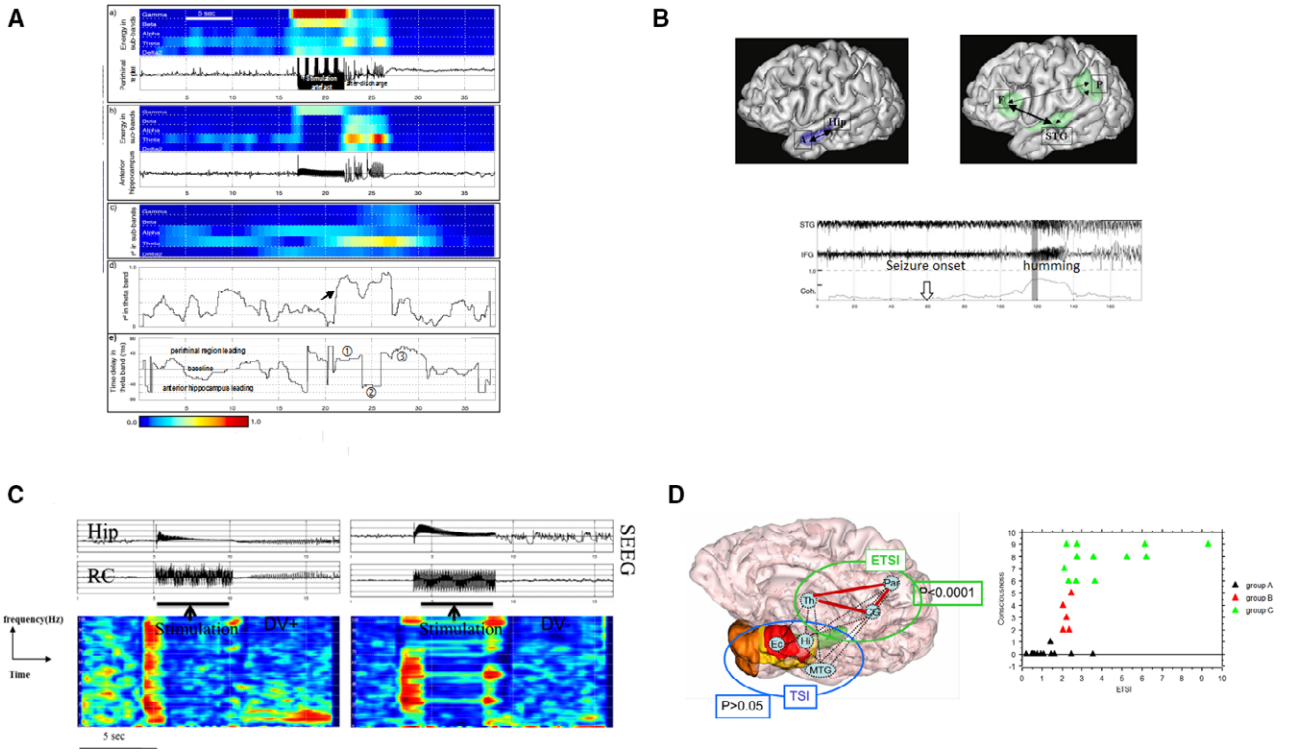

Figure 6.

Examples of changes in Fc affecting propagation network and the production of semiology. (**A**) Depth-EEG signal recorded from the perirhinal cortex and the hippocampus before ($t < 17$ s), during ($17 \text{ s} < t < 22$ s), and after ($t > 22$ s) electrical stimulation of the perirhinal cortex and distribution of the normalized average energy in various frequency bands. Theta activity is predominant during the afterdischarge (AD). Evolution of correlation values in the theta band as a function of time. Correlation values rise during the AD (arrow). Evolution of the causality relationship between signals recorded from the perirhinal and anterior hippocampus as a function of time. Causality relationship values show a complex interaction between perirhinal and anterior hippocampus during the AD from Barbeau et al.[100]. (**B**) Time-frequency representation of EEG correlation changes after stimulation of the rhinal cortex (RC) inducing "déjà vu" (left, DV+) and stimulation not inducing "déjà vu" (right, DV-). DV+ stimulation is associated with an increased correlation of signals between RC and hippocampus (Hip) predominant in theta frequency (adapted from Bartolomei et al.[101]). (**C**) In patients with humming automatism during seizures, coherence calculated between SEEG signals showed significant increase between prefrontal cortex and the superior temporal gyrus (adapted from Bartolomei et al.[102]). (**D**) Schematic spatial representation of Fc changes in TLE seizures with loss of consciousness compared to seizures without loss of consciousness estimated from SEEG signals. Significant changes in connectivity values (ETSI, extratemporal synchrony index) are observed in extratemporal cortex and particularly between the thalamus and parietal cortex. Right part: Relationship between synchrony values (ETSI) and the loss of consciousness estimated by the "seizure consciousness scale" (CSS). This relation follows a sigmoid curve suggesting a nonlinear bistable function for consciousness (adapted from Arthuis et al.[88]).

more recently extended to extratemporal seizures,[105,106] where a nonlinear relationship has been also observed between the level of connectivity between frontal and parietal cortex and degree of LOC.

In contrast to the above examples of excessive synchronization associated with specific semiologic expressions, desynchronization may also be important in the genesis of ictal symptoms, notably in paralimbic system seizures characterized by apparent fear-related behavior with massive decrease of synchrony between orbitofrontal cortex and amygdala being observed in concordance with the explosive onset of behavioral change.[107] This transient functional uncoupling could thus disrupt emotional regulation, thereby leading to the release of altered behavior.

The Epileptic Brain Shows Altered Functional Connectivity during the Interictal State

In focal epilepsies, the interictal state is characterized by the occurrence of electrophysiologic biomarkers of the pathologic process. The most evident anomalies are epileptic spikes that are usually closely related to the EZ (also referred to as the primary "irritative zone") but can also appear in regions remote from the EZ (probably mapping propagation networks, often referred to as "secondary irritative zone"; see Bettus et al.[11] for definitions). A recent

SEEG study investigated the distribution of interictal epileptic spikes (based on a spike frequency index, SI) and the topography of the EZ (based on the epileptogenicity index, EI) in patients with focal neocortical epilepsies.[108] In this study, good agreement between maximal EI and maximal SI values was found in 56% of cases (reaching 75% in cases of FCD). Thus many patients have some dissociation between those regions showing pronounced interictal spiking activity and those showing high epileptogenicity. Different investigations using SEEG have shown that interictal spikes are distributed within specific subnetworks in the brain. Due to the very short times of propagation of interictal activity across brain regions,[109] methods have been proposed to quantify the co-occurrence of spikes in distant areas. Thus Bourien et al. quantified the cooccurrence of spikes in mesial TLE,[110] showing that (1) spikes were distributed in mesial temporal regions and (2) in half of patients, independent networks in neocortical regions could be demonstrated. This kind of network distribution of spiking activity has also been observed in extratemporal epilepsies (Fig. S1).[111]

A study using the mean phase coherence algorithm revealed that areas of elevated local synchrony overlap with the EZ, suggesting that high local synchrony may be a marker for epileptogenic cortex.[112] Furthermore, this study suggested correlation between the resection of area of high local synchrony and good surgical outcome. Similarly, another study confirmed this result in a larger population of patients with ECoG recordings of lateral temporal lobe, for whom the removal of the sharply defined clusters of high-synchronized structures was correlated with postsurgical seizure outcome.[113] Only one study had the opportunity to compare epileptic to nonepileptic patients, using ECoG recordings from patients with neocortical epilepsies and facial pain,[114] showing that structures within the EZ are functionally disconnected from surrounding structures in comparison with nonepileptic patients. Wilke et al., using ECoG recordings of neocortical epilepsies, investigated network topology modification.[63] They showed that betweenness centrality calculated in the gamma band from the interictal period correlated well with betweenness centrality calculated from the ictal period.

The previous study used ECoG recordings and thus reported localized areas of high synchronization but with limited possibility to perform more large-scale analysis. In this respect, SEEG is more suitable for sampling distant brain areas, and some recent studies have addressed this question. First, local increase in interictal synchrony was shown in structures within the EZ in patients with MTLE.[115] An SEEG study estimated functional connectivity between mesial temporal structures by comparing a group of patients with MTLE to a "control" group including patients with extratemporal seizures.[116] Interdependencies between artifact-free signals from at least two areas of interest (amygdala, anterior hippocampus, entorhinal cortex, and posterior hippocampus) were estimated over a 30 min resting state period. Results showed that functional coupling was enhanced within the mesiotemporal structures belonging to the EZ (Fig. 7A). Using similar methodology in patients with TLE, another study confirmed the increase of functional connectivity between the structures belonging to epileptic regions (epileptogenic and irritative zones) relative to regions spared by epileptiform discharges.[11] More interestingly, effective connectivity showed that functional connectivity was oriented preferentially from the EZ to remote areas spared by electrical abnormalities during the interictal state (significantly positive mean directionality indexes). Notably, this functional connectivity enhancement was to a large part independent of the occurrence of interictal spiking. Notably these results are like those obtained in the rat kindling model,[117] where increased coherence between temporal and frontal regions was found after completion of the kindling procedure, suggesting that increased interictal EEG synchrony is a baseline property of epileptogenic structures.

These various findings highlighting the link between abnormal synchrony and epileptogenicity could have relevance for potential therapeutic approaches. Recent studies suggest that decreasing abnormal interictal synchrony could be a mechanism of action for neurostimulation, in particular for vagus nerve stimulation (VNS). Indeed, we recently found that responder patients disclosed decreased SEEG[118] Fc during interictal periods, in particularly during ON stimulation. A worsening effect has been suggested when increased Fc is induced by VNS.[118]

Graph analysis of interictal networks estimated from SEEG recordings in patients with mesial TLE[62] showed significantly more regular configuration in the temporal lobe compared to non-MTLE patients. This result was interpreted as increased local connectivity with slightly decreased long distance connections. The fact that the interictal state in patients with focal epilepsy could be characterized by a more regular configuration was also suggested by other approaches such as MEG.[119,120] The clinical significance of this state is unclear but it could be a biomarker of the epileptic process.

Finally, it is worth noting that many of the connectivity studies in focal epilepsies have used fMRI to investigate the network properties of the epileptic brain during the interictal period.[38] These studies have shown distributed changes including both increased and impaired connectivity with links to pathologic and potentially compensatory processes in epilepsy. To date, only one study has compared intracerebral EEG and fMRI BOLD connectivity estimated from the same location within the same individuals,[11] finding a trend to fMRI-Fc reduction in the EZ and primary irritative zone (vs. noninvolved regions), whereas the SEEG-Fc was increased. This apparent discrepancy needs to be verified in larger cohorts and/or in simultaneous recordings; its origin is not well understood. Altered neurovascular coupling has been proposed as a potential explanation.[11]

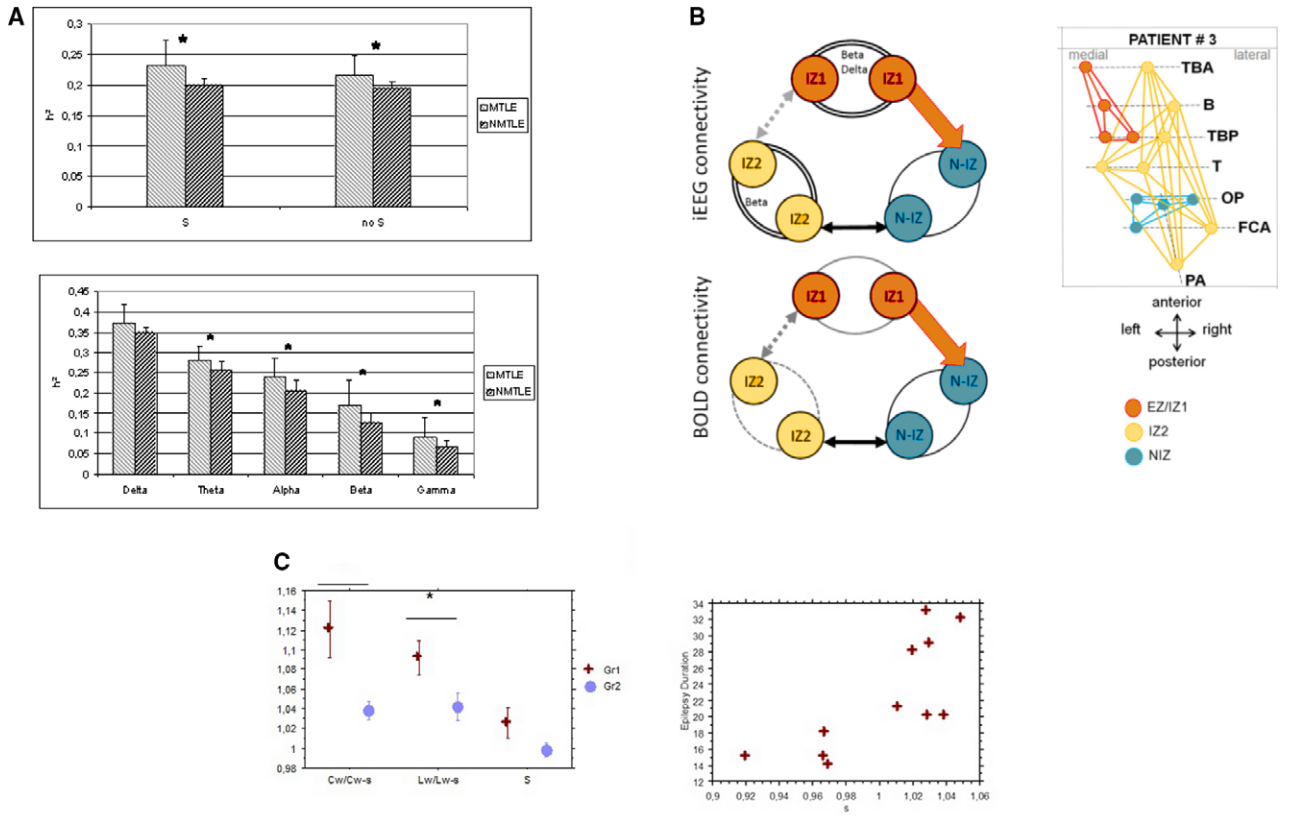

Figure 7.

Interictal SEEG connectivity. (**A**) Illustration of the higher values in Fc (h^2 values) (EEG broad band [0.5–110 Hz]) found in MTLE patients in comparison with a control group (non-MTLE [NMTLE]). h^2 values were computed from native SEEG signals (S, with spikes) or were computed on SEEG signals in which interictal spikes were withdrawn (No S). Correlation values are significantly higher in the MTLE group for both conditions (*, $p \leq 0.01$). Lower part: mean h^2 values from mesial temporal lobe SEEG signals in each frequency subband. Correlation values are significantly higher in the MTLE group for theta, alpha, beta, and gamma bands (*, $p \leq 0.01$). (**B**) Comparison between SEEG and fMRI/C Fc in the same patients.[11] Schemes of basal functional (h^2) and effective (direction index) connectivity during the interictal period. Circles represent regions of interest from different zones: IZ1, primary irritative zone; IZ2, secondary irritative zone; N-IZ, nonirritative zone. Functional connectivity (Fc, h^2 correlations) is estimated from the same regions in the patients from SEEG signals or fMRI BOLD signals. Interactions are illustrated (right part) for one patient. Curved lines represent Fc between 2 regions of interest (ROIs) in the same zone. N-IZ to N-IZ connectivity is considered as "normal" functional connectivity (FC). Compared to this reference, (1) double curved lines represent significantly increased FC between ROIs in other zones, (2) gray and dotted curved lines represent significantly decreased FC between ROIs in other zones, and (3) gray curved lines represent trend of decreased FC between ROIs in other zones. Between-zone functional connectivity: Arrows represent effective connectivity between zones. Unidirectional and red arrows correspond to significant direction indices (effective connectivity) between zones. Double arrows correspond to nonsignificant direction indices between zones. Gray and dotted double arrows represent significantly lower functional connectivity (h^2 values) between IZ1- and IZ2 compared to h^2 values between other zones. (**C**) A study of graph parameters estimated from Fc analysis during the interictal state in patients with MTLE. Fc is estimated between temporal lobe regions using the synchronization likelihood method (SL). Increased values are observed for the mean normalized cluster coefficient Cw/Cw-s and the averaged path length (Lw/Lw-s) in the MTLE group (Gr1 [red cross] in comparison with non-MTLE group [gr2, blue circles]). Error bars correspond to standard error of the mean. (*) indicates significant differences between the two groups ($p < 0.05$). Right part: relationship between epilepsy duration and small world index (S index). This relation indicates a significant trend between this two parameters (Spearman correlation test, $p = 0.02$).

Conclusions

Accurate description of the brain regions involved in seizure genesis is a crucial objective in the context of epilepsy surgery. Since the early works of Bancaud and Talairach using SEEG, multiple approaches have been developed to study the spatiotemporal oscillatory dynamics of brain networks engaged in epileptogenic processes. These studies have shown that the EZ may be distributed in specific systems. The efforts to quantify the complex phenomena that rule the spatiotemporal organization of the EZ are laudable, but how these concepts may be useful in clinical practice

remains uncertain and underapplied.[121] It is still unknown whether these concepts could be used to improve surgery procedures via, for instance, tailored and minimally invasive curative surgery based on specific disconnection or multiple nodal targeting.

In this context, new perspectives are offered by the introduction of large-scale network models that aim at decoding and explaining the mechanisms underlying the generation of seizures and epileptic activities (for review see Wendling et al.[122]). In addition, such macroscopic models on a whole brain scale (such as the Virtual Brain model) can be used to validate or invalidate the conceptual issue of epileptogenicity extension through structural connectivity of specific neural systems. The first "virtual epileptic patient" has been published recently,[19] showing that mathematical models of seizure genesis combined with the structural connectivity data of the patient may provide a realistic description of epileptogenic network dynamics on an individual level. More recently, in a pilot study we demonstrated the favorable correlation between model prediction and surgery outcome. Indeed, negative surgery outcome was correlated with surgery that was not performed in line with model predictions.[123]

This kind of approach offers the perspective of modeling the impact of minimally invasive tailored resection, surgical deconnexion, or neurostimulation in a patient-specific context by testing several surgical options in each individual. In the future, this could dramatically alter prediction of the outcome of epilepsy surgery and help us to better understand the causes of surgical failure, as well as pave the way to more precisely targeted and calibrated neurostimulation. Novel therapeutic approaches in the aim of judicious "network disruption" for an individual patient may also thus become possible in the future.

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Disclosure

None of the authors has any conflict of interest to disclose concerning the present publication. 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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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1 (**A**) Interictal co-occurrence networks in SEEG recorded interictal activity in MTLE patients (Bourien et al., 2005). Upper part: Asterisks indicate automatically detected interictal events. Lower part: Topographic display of extracted subsets of co-activated structures (SCAS) in seven patients. A schematic representation is used in which 13 explored structures are positioned over a circle (upper half circle: lateral structures of the temporal lobe; lower half circle: lower structures of the temporal lobe). SCAS are denoted by closed contours. Gray level indicates occurrence frequency (gray scale in upper left box, quantification step of 5%). (**B**) Comparison between interictal networks of MEG and SEEG for the same patient (Malinowska et al.,[36]). Leading nodes are shown with circles, in the sense of the delay measure, the NIE (number of independent events) measure, or both. The SEEG graph is more extended than the MEG graph, but shares common regions in the parietooccipital junction and posterior temporal lobe. One leading node is consistent across modalities (temporal posterior region).