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Review articles

Functional connectivity of interictal iEEG and the connectivity of high-frequency components in epilepsy

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ABSTRACT

Epilepsy is a disease of altered brain networks. The monitoring and analysis of functional connectivity and network properties can yield a better understanding of the underlying pathology, and improve treatment and prognostics. Identifying hub network regions has been in the spotlight of network neuroscience studies in epilepsy, as monitoring these areas can provide a perspective of the network's local and global organization. Functional network analysis can be especially useful in Medically Refractory Epilepsy (MRE) cases, where surgical intervention is necessary for seizure relief. In such cases, the delineation of the epileptogenic zone, which represents the surgical target, is a very crucial procedure, which can be enhanced by understanding the underlying network topology. In this review, we will explore the expanding body of literature on functional connectivity of interictal intracranial electrophysiologic data, focusing on the interpretation of network properties, global or local, for identifying epileptogenic tissue. We will emphasize functional connectivity at high frequencies (above 80 Hz), as during the past decade High-Frequency Oscillations (HFOs) have been increasingly recognized as a promising biomarker of the seizure onset zone. We will conclude the review with an assessment of current limitations and a discussion of future research paths.

1. Introduction

With over 2.4 million people being affected every year, epilepsy is one of the most common and well-studied neurological disorders (Ahmedt-Aristizabal et al., 2017), accounting for 5% of disability-adjusted life-years for neurological diseases (San-Juan and Rodríguez-Méndez, 2023). Most of the cases start in childhood, consistent with the developing brain's increased propensity for seizures (Stafstrom and Carmant, 2015). Some of the classic symptoms include seizures, unusual sensations, generalized convulsions, and very often loss of awareness. Focal seizures, in particular, account for up to 61% of patients with epilepsy and are linked with an elevated risk of injury and premature death compared to the general population (Ioannou, 2022).

Advancing the diagnostic and therapeutic procedures for epileptic patients requires a good understanding of the neurophysiological underpinnings that cause the generation and propagation of seizures in the epileptic brain (Kramer and Cash, 2012). Despite the fact that for many years clinicians and researchers sought answers in the molecular, anatomical, and cellular changes involved in epileptogenesis, the focus of most recent literature has shifted towards the understanding of epilepsy as a network disease (San-Juan and Rodríguez-Méndez, 2023; Bartolomei, 2017; Stacey, 2020). The concept of epileptogenic networks dates back to the 1960 s when early stereoenchephalography (SEEG) studies from Bancaud and Talairach demonstrated seizure generation from structures quite distant from the epileptogenic lesion (Talairach and Bancaud, 1966). There is now a plethora of evidence supporting the idea that seizures are directly linked with the abnormal synchronization of distant structures, mainly derived from functional connectivity studies (Jiruska et al., 2013; Guye, 2006; Varotto et al., 2012). Studying the spatiotemporal dynamics of the epileptic network can provide important insights into the anatomical distribution of the epileptogenic process, which is significantly important in the context of epilepsy surgery (Bartolomei, 2017), the most prominent therapeutic solution for patients with MRE (Dwivedi, 2017; Ryvlin et al., 2014).

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Intracranial recordings, either electrocorticography (ECoG) or SEEG, have advanced research in this area due to their high spatial resolution (mm^3 level) and outstanding temporal resolution (millisecond scale). Targeting key nodes (hubs) in the network, which are crucial for its organization and functioning, can lead to better clinical practices and more efficient surgical treatments, through minimally invasive tailored resections. Such practices could be complimentary to the standard presurgical neuroimaging procedures, like analysis of high-resolution MRI, high-density electroencephalography (EEG), and fMRI data, recorded at both ictal and interictal periods (Ryvlin et al., 2014). The interictal stage in particular, has been well studied, as it is connected with the occurrence of electrophysiologic biomarkers such as interictal epileptiform discharges (IEDs) and High-Frequency Oscillations (HFOs), while also presenting practical advantages (reduced amount of recorded data) compared to the unpredictable ictal recordings. Functional connectivity during this period has been reported as particularly altered in previous works(Lagarde et al., 2022). Therefore, it would be interesting to discuss the recent advancements in the field of interictal functional alterations of intracranial electroencephalography (iEEG), and explore their potential in epileptogenic zone (EZ) identification and postsurgical outcome prediction. We will also highlight the potentials of high-frequency graphical networks ($>$ 80 Hz) as an alternative methodology to extract information for the EZ, instead of adopting the classical interpretation of HFOs (in terms of their rate), the use of which comes with inherent issues (see HFOs in epilepsy section).

We first introduce the reader to the concepts of MRE, epilepsy surgery, and HFOs, and then continue with discussing the literature on functional connectivity of ECoG and SEEG in both the conventional and the high-frequency band.

2. Medically refractory epilepsy and surgical treatment

Despite the fact that most epilepsy patients are successfully treated with antiepileptic drugs (AED), such as Valproic Acid (VAP) (Devinsky, 2018), Carbamazepine (CBZ) (Kuo, 1998), and Benzodiazepines (BZD) (Greenfield, 2013), it is estimated that around 30% of the cases suffer from MRE, as they present poor post-pharmacological control and continue having symptoms (Kwan and Brodie, 2000), (Sander, 2003). The pathological reasons behind MRE have not yet been completely understood. However, there are several hypotheses behind pharmacoresistance in epilepsy. The “transporter” theory postulates that the overexpression of efflux transporters present in the blood-brain barrier can reduce the penetration of anti-seizure medications into the brain, limiting their effectiveness (Sisodiya et al., 2002). Moreover, the “network hypothesis” supports that neuron degeneration and synaptic network remodeling, due to seizures, can contribute to the generation of an altered neural network, which prevents AEDs from reaching their target, eventually leading to MRE (Bazhanova et al., 2021). Despite the uncertainty around the pathogenesis of MRE, epilepsy patients with recurrent seizures should be referred to a full-service epilepsy center as soon as possible. This is due to the fact that MRE patients are at very high risk of adverse consequences, ranging from behavioral, interpersonal, and social inabilities to increased risk for injuries and premature mortality due to either seizure-related accidents or due to sudden unexpected death in epilepsy (SUDEP) (Mohanraj et al., 2006; Engel, 2016). Nevertheless, less than 1% of patients with MRE are evaluated at an epilepsy center (Engel, 2016), with 10–50% being surgical candidates (Baumgartner et al., 2019). In such cases, a multidisciplinary team of experts typically evaluates that epilepsy surgery (ES) represents the only available treatment to achieve seizure freedom.

2.1. Epilepsy surgery (ES)

The basic idea behind epilepsy surgery is the complete resection or disconnection of the Epileptogenic Zone (EZ), which is defined as the cortical region where habitual seizures originate and at the same time removing the minimal amount of tissue in order to achieve seizure relief (Lüders et al., 2006; Rosenow and Lüders, 2001). The only way to determine whether epilepsy surgery is successful is to look at the patient's postoperative results: if the EZ was accurately diagnosed and removed without harming the functionally important eloquent cortex, the patient will be seizure-free with few to no functional losses. Subsequently, a thorough presurgical evaluation to clearly delineate the EZ and the essential areas to be spared is crucial for the outcome of the surgery. However, this is a challenging procedure, especially in cases with no specific histopathological causes (like hippocampal sclerosis, tumors, etc.), and due to the fact that no diagnostic technique is so far able to clearly define this zone (Jobst and Cascino, 2015).

A first attempt to localize the EZ combines information from noninvasive recordings both during the ictal (single-photon emission computed tomography (SPECT), high-density EEG (HD-EEG), or electrical source imaging (ESI)) and the interictal periods (magnetoencephalography (MEG), magnetic source imaging (MSI), and HD-EEG). However, in many patients, the delineation of the EZ can not be sufficiently accurate based solely on these non-invasive techniques, or the functionally important cortical areas are in very close proximity to the proposed resection site. In such cases, intracranial EEG is employed. It can be applied by using subdural strip and grid electrodes (ECOG) or a combination of depth and subdural electrodes, after open craniotomy (CEEG). While strips (Fig. 1a) and grids (Fig. 1b) of subdural electrodes provide a large coverage over the bare surface of the cerebral cortex, they are often implanted in one hemisphere and do not reach deeper brain structures (e.g., hippocampus or insula) (Parvizi and Kastner, 2018). By comparison, there are cases where only multi-channel depth electrodes are placed stereotactically (SEEG) (Fig. 1c), through a twist drill hole or burr hole under general anesthesia, with this type of monitoring being increasingly appealing to many epilepsy centers due to its less invasive nature and increased comfort for the patients (Baumgartner et al., 2019). Such electrodes can also enable bilateral monitoring of superficial and deep cortical structures (Bartolomei, 2017).

2.2. Seizure onset zone and interictal biomarkers

Despite the large number of available imaging modalities (either invasive or noninvasive), there is no gold standard diagnostic biomarker for the localization of the EZ. Fig. 2 illustrates the most commonly defined zones during the presurgical evaluation of a patient. In clinical practice, the most established biomarker is the seizure onset zone (SOZ) (Balaji and Parhi, 2022), especially when defined by iEEG (Matarrese, 2023). Epileptologists define the SOZ by interpreting the waveform patterns at seizure onset but also pay great attention to

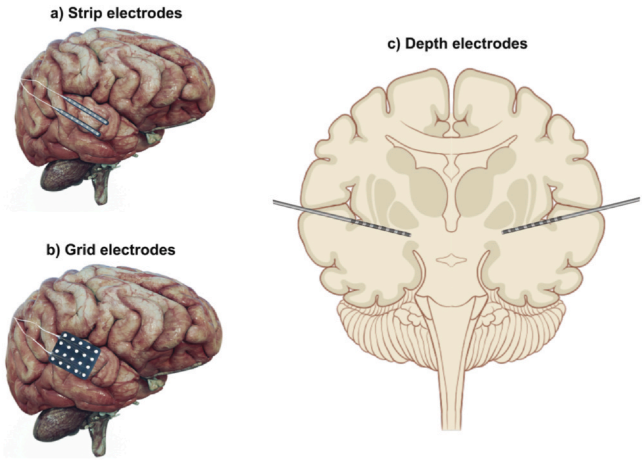

Fig. 1. Intracranial electrodes used for the monitoring of epilepsy patients. a) Strip electrodes (ECoG), b) Grid electrodes (ECoG), and c) Depth electrodes.

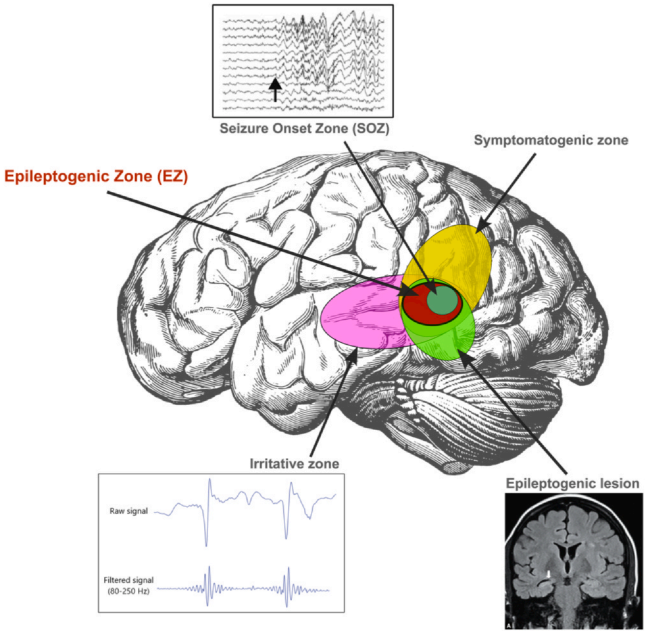

Fig. 2. Different cortical areas defined through both invasive and non-invasive neuroimaging during the presurgical evaluation stage. The location and relative size of each zone vary across different clinical cases. Irritative zone: area of the cortex that generates Interictal Epileptiform Discharges (IEDs), Epileptogenic lesion: structural brain abnormality that is causally related to epilepsy, Symptomatogenic zone: area of the cortex that is functionally abnormal during the interictal period, Seizure-Onset Zone (SOZ): area where clinical seizures originate on ictal recordings.

interictal events like interictal epileptiform discharges (also known as interictal spikes) and high-frequency oscillations (HFOs).

Interictal spikes have been extensively studied and widely recognized as an important biomarker of epileptogenic activity (Lee et al., 2013). As relatively large and prominent events, they are easy to detect in an iEEG (Marsh, 2010), while they can also be seen in non-invasive modalities like scalp EEG and MEG (Abd El-Samie et al., 2018). They are propagating events and they can be present over large cortical areas (Tamilia, 2018; Tomlinson et al., 2016), while sites of spike onset correlate with the SOZ (Hufnagel et al., 2000; Lai et al., 2007) and resection of such sites is associated with good patient outcome post-operatively (Matarrese, 2023; Alarcon, 1997). However, spikes suffer from low specificity to the EZ, as the cortical area that they designate can often be larger than the actual EZ and thus can overlap with the healthy surrounding tissue (mainly due to their propagation properties) (Matarrese, 2023). It is also established, that interictal HFOs are better and more accurate epilepsy biomarkers compared to spikes (Tamilia, 2018; Jacobs et al., 2008; Jacobs, 2010), as they are believed to be more closely related to the epileptogenic process. HFOs and their properties are discussed in the next section.

3. High-frequency oscillations in epilepsy

High-frequency oscillations (HFOs) are local oscillatory field potentials, with frequencies ranging from 80 Hz to 500 Hz, typically divided into ripples (80–250 Hz) and fast ripples (250–500 Hz) (van ’t Klooster, 2015), (Zijlmans et al., 2012). Their association with epilepsy has been studied for over 15 years now, indicating that HFOs are an important biomarker of epileptogenicity. The neuronal and circuit substrates of HFOs remain elusive (Cepeda, 2020), however, there are numerous theories, mainly focusing on the synchronized firing of principal cells within discretely located neuronal clusters (Jiruska, 2017), and the importance of GABAergic interneurons (Cepeda, 2020). No matter what the underlying cellular mechanisms are, HFOs are now well-described electrophysiologic events, closely linked to the epileptogenic tissue. Research in this area has demonstrated that the presurgical diagnosis (Cho et al., 2012; Kerber, 2014), and the surgical outcome (van ’t Klooster, 2015; Akiyama, 2011; van Klink, 2014) of patients with MRE may be improved by removing the tissue that generates HFOs. Despite these encouraging results, there is still strong debate on whether HFOs are suitable for the identification or monitoring of epilepsy in clinical settings (Chen et al., 2021), but this is mainly due to the lack of an established consensus and available equipment (i.e iEEG recordings, analysis tools, etc.) for the recording and interpretation of HFOs in many epilepsy centers. A major drawback that prohibits HFOs from entering clinical practice is that the only universally acceptable technique for detecting them is through visual inspection of the data. This is a very time-consuming procedure, which should be performed by trained epileptologists with experience in the detection of these very specific oscillations. A striking example is that for just 10 min of a 10-channel iEEG recording, a clinician needs almost 10 h to accurately detect the HFOs (Sciaraffa et al., 2020). In addition, visual detection is also subject-dependent and prone to errors due to human factors. For these reasons, the development of automatic HFO detectors has drawn a lot of attention during the past ten years, and since there is not an established gold-standard algorithm yet, it remains a focus of ongoing research (Papadelis, 2016; Quitadamo et al., 2018; von Ellenrieder, 2016; Wong, 2021). The fact that the accuracy of the HFO detectors can be easily jeopardized by poor parameter optimization and the need for constant visual validation every time a detector is used in a different dataset pose limitations for using such tools, especially during everyday clinical practice. In addition, it is well known that the main use of such detectors is for interpreting the discovered HFOs in terms of their rate (HFO events per minute) in each iEEG channel and using this rate as a biomarker for the SOZ. Specific HFO characteristics could also act as alternatives to the HFO rate for measuring the epileptogenicity of different areas. For example, HFO amplitudes and frequencies were found to be significantly different between areas covering epileptic tissue compared to areas outside the SOZ (Malinowska et al., 2015). Similarly, Pail et al., (Pail et al., 2017) reported reduced HFO duration and elevated HFO amplitude inside the SOZ compared to peripheral areas. Finally, in a recent study, Charupanit et al., (Charupanit et al., 2020) found that anomalous high-frequency events had significant differences in the amplitude of the events, inside vs. outside the SOZ, despite the similarity in their rates.

3.1. *Features of iEEG in the high frequencies as an alternative*

Despite the fact that the literature is dominated by discrete detection of HFOs when assessing their potential in localizing epileptogenic tissue, other techniques have also been proposed, mainly regarding the computation of specific measures in the entire length of the iEEG signal at high frequencies, and not focusing on the distinct events per se. These methods have some methodological and practical advantages over those accounting for distinct HFOs. They are not constrained by the lack of a universal agreement on the specific characteristics of HFOs, which frequently vary across the different research teams and epilepsy centers. In addition, as these methods do not account for the semiology of distinct events, they usually include a smaller number of interdependent parameters that need to be optimized. Computing specific metrics in the whole extent of the signal could also be more efficient, requiring less computational time compared to automatic HFO detectors. For example, in the work of Mooij et al., the authors proved that the skew of the distribution of power values was higher in the SOZ compared to non-SOZ areas in three frequency bands (5–80 Hz, ripples, and fast-ripples) (Mooij et al., 2020). In another study, Akter et al., generated a novel epileptic channel identification system by assessing the predictive value of 12 different statistical features (6 purely statistical and 3 entropy features) computed from High-Frequency Components (> 80 Hz) for identifying the SOZ (Akter, 2020). Significant interest has also been shown in techniques that quantify the cross-frequency coupling between high-frequency amplitude and low-frequency phase, most commonly through the modulation index (MI). An early study by Weiss et al., found that the coupling between amplitude in the frequency range of 80–150 Hz with low-frequency (1–25 Hz) phase was significantly elevated in the "ictal core", which defines the regions that fully participate in a seizure, compared to peripheral regions (Weiss, Dec. 2013). Moreover, Ibrahim et al., showed that coupling between high-frequency amplitude and alpha and theta phase was higher inside the SOZ (Ibrahim, Jan. 2014), something that was also supported later by Motoi et al., who reported a higher MI z-score in the SOZ compared to nonepileptic regions (Motoi, 2019). The MI was also used by Guirgis et al. (delta and theta modulation on HFOs (30–450 Hz)), who used eigenvalue decomposition to identify an "area of interest", and found that when this area was not fully removed during the epilepsy surgery, patients were more likely to have recurrent seizures (Guirgis et al., 2015).

4. Functional connectivity and networks in epilepsy

In order to discuss the research on interictal functional connectivity in focal refractory epilepsy we group the studies as 1) studies assessing the connectivity measures themselves, and 2) studies that interpret different metrics of the functional network after applying graph theory. Cases where information from both levels is concerned are attributed to the discussion of the corresponding group each time. We focus only on studies that used intracranial recordings, without making a distinction between ECoG and SEEG-based works. However, it is noteworthy that SEEG is generally preferred over ECoG, due to its connection with lower morbidity rates (Jehi, 2021; Katz and Abel, 2019; J and Mullin, 2016), better coverage of subcortical tissue, and the ability to record information from both hemispheres (Lagarde et al., 2022). This is why the larger body of literature concerns this type of recording.

4.1. Connectivity measure level studies

A variety of quantitative methods have been used to assess the synchronization between neuronal populations of different cerebral areas using interictal iEEG. One of the first attempts was by Towle et al., who found elevated levels of coherence in the area of the epileptic focus in 6/7 temporal lobe epilepsy (TLE) patients (and 8/9 focal epilepsy patients in total), using ECoG recordings (Towle, 1998). A similar study by Morman et al., who computed the mean phase coherence on bilateral SEEG recordings of 17 TLE patients, demonstrated increased levels of interictal mutual synchronization in the EZ compared to the non-focal side (Mormann et al., 2000). This metric was also employed in an SEEG study by Schevon et al., who showed that local hypersynchrony (LH) regions (areas with significantly increased synchrony) had a significant association with the clinically defined EZ, however not overlapping precisely but rather being adjacent to it, in 9 neocortical epilepsy patients (Schevon, 2007). Later studies confirmed this relationship between hypersynchrony and the EZ, using a combination of ECoG and SEEG. For example, Dauwels et al. used different functional connectivity (FC) metrics (correlation coefficient, phase synchrony, magnitude coherence, and Granger causality) to study the neural synchrony in 6 patients (mainly TLE) sampled with purely SEEG or a blend of SEEG and ECoG electrodes. They demonstrated strong overlaps between localized synchrony and the epileptic focus in 5/6 patients (Dauwels et al., 2009). These results propose that LH can be a promising biomarker of the epileptic tissue. However, most of these studies mainly sampled the temporal lobe, as mostly TLE cases were assessed.

Other studies have proceeded on a more comprehensive brain coverage mainly through the SEEG modality, recording both temporal and extratemporal neocortex regions. For instance, Bettus et al. (Bettus, 2008) used SEEG to compare the FC (nonlinear correlation coefficient h^2) in mesial temporal structures (hippocampus, entorhinal cortex, and amygdala) of 21 patients with Mesial Temporal Lobe epilepsy (MTLE) to a "control" group of 14 non-MTLE patients (frontal, lateral temporal, and occipital lobe epilepsies). This study showed significantly increased connectivity in the MTL group, a result that was later replicated by Bartolomei et al. who used the synchronization likelihood to study the functional alterations in a similar cohort of patients (11 MTLE vs. 8 non-MTLE patients) (Bartolomei et al., 2013).

A recent large-scale study by Lagarde et al. (Lagarde, 2018) used dens SEEG coverage in 59 focal epilepsy patients (various types) to study the connectivity within and between different epileptogenic regions (defined with the help of the epileptogenic index during the ictal period). The connectivity within each region, namely the Epileptogenic Zone (EZ), the Propagation Zone (PZ), and the Non-Involved Zone (NIZ), was found to gradually decrease from the former to the latter, while the EZ was preferentially linked to the PZ compared to the NIZ, supporting the notion that FC can track the flow of epileptic activity and describe its organization. The same connectivity profile (decrease of connectivity from the EZ to the NIZ) was reported by Narasimhan et al., who comprehensively studied the interdependence between SEEG signals of 25 focal epilepsy patients (mostly MTLE), by employing several directed and non-directed connectivity measures (imaginary coherence, mutual information, partially directed coherence, and directed transfer function (DTF)). An interesting addition of this study was the assessment of the predictive value of interictal FC in defining epileptogenic structures, for which the authors found that by combining the different directed and undirected measures accuracies of up to 84.7 ± 5.5% could be achieved (N. S, 2020).

The studies discussed above, which are summarized in Table 1, consistently highlighted the correlation between local clusters of increased FC (from a range of different measures) with the EZ, and the functional isolation of the EZ from the NIZ during the interictal period.

4.1.1. Interictal FC and surgical outcome

Several studies have associated FC changes with the prediction of surgical outcome. Schevon et al., have demonstrated that complete resection of LH regions improves clinical outcome (Schevon, 2007) something that was challenged by Ortega et al. a year later, who by using three FC metrics (linear correlation, mutual information, and phase synchronization) in ECoG data from 29 TLE patients could not find a connection between the resection of LH clusters and surgical outcome (Ortega et al., 2008). However, this could be due to the fact that the majority of the patients were treated with anterior temporal lobectomy, while according to Lagarde et al. (Lagarde et al., 2022), ECoG is mainly sensitive to the dynamics of the lateral temporal neocortex. More recent SEEG studies, using either linear correlation (Shah, 2019) or imaginary coherence (Goodale, 2020) to measure FC, have confirmed the early results by Schevon et al. (Schevon, 2007), as good-outcome patients were found to have significantly increased interdependences within the resection zone compared to bad-outcome cases. Worse outcomes have also been associated with higher values of FC (h^2 measure) in the NIZ in good vs. poor outcome patients (Lagarde, 2018). Finally, Jiang et al., have shown that a larger information flow asymmetry is linked with better surgical outcomes (Jiang, 2022).

4.2. Graphical network level studies

A number of studies have advanced the FC analysis of iEEG, using mathematical tools such as graph theory, to generate functional networks with the iEEG channels as nodes and the connectivity values between them as edges. Local topology analysis (at the node or set of nodes level) in these networks could provide crucial information for the localization of the EZ. For instance, Wilke et al. calculated the betweenness centrality (BC) in a DTF-based network in a cohort of 25 focal epilepsy patients (ECoG recordings in all) (Wilke et al., 2011). Their analysis demonstrated that, during the interictal period, BC changes in the gamma frequency band correlated with the EZ. Other

Table 1

Summary of studies on interictal functional connectivity (FC) that used the FC measure itself to describe the epileptogenic zone.

Authors	Patient population	Connectivity metric	Frequency range	Findings / Main results
		Conventional Frequencies (< 100 Hz)		
Towle, 1998	25 patients (12 with TLE)	Coherence	1–32 Hz	Localized regions of high FC observed over the EZ
Mormann et al., 2000	17 patients with TLE	Mean phase coherence	0.5–85 Hz	Increased levels of FC in the EZ compared to the non-focal side
Schevon, 2007	9 patients with neocortical epilepsies	Mean phase coherence	0.1–54 Hz & 0.5–65 Hz	Areas of local hypersynchrony overlapping with the EZ (not completely, rather being adjacent to it)
Bettus, 2008	35 patients (21 with MTLE and 14 with non-TLE)	Nonlinear correlation coefficient (h^2)	0.5–97 Hz	Significant increase of connectivity in mesial temporal structures when these regions belong to the EZ
Dauwels et al., 2009	6 patients with focal epilepsy (mainly TLE)	Correlation coefficient, Phase synchrony, Magnitude coherence, Granger causality	4–30 Hz	Strong overlap between areas of localized synchrony and the epileptic focus (EZ)
Bartolomei et al., 2013	19 patients (11 MTLE & 8 non-MTLE)	synchronization likelihood	0.5–90 Hz	FC increases in temporal lobe regions when these regions overlap with the EZ
Lagarde, 2018	59 patients with focal epilepsy (20 with TLE)	nonlinear correlation coefficient (h^2)	0.5–80 Hz	FC values decrease from the EZ to PZ to NIZ (EZ < PZ < NIZ)
N. S, 2020	25 patients with focal epilepsy (18 with MTLE)	imaginary coherence, mutual information, partially directed coherence, directed transfer function	8–12 Hz	Decrease of the FC: EZ < PZ < Iritative Zone < NIZ
		High Frequencies (> 100 Hz)		
Jiang, 2022	27 patients with focal epilepsy (23 with TLE)	directed transfer function, cross-frequency directionality	1–250 Hz	Information flow from high frequencies in the NIZ to low frequencies in the EZ

Table 2

Summary of studies on interictal functional connectivity (FC) that used graphical network measures to describe the epileptogenic zone.

Authors	Patient population	Connectivity metric → Network measure (s)	Frequency range	Findings / Main results
		Conventional Frequencies (< 100 Hz)		
Wilke et al., 2011	25 patients with focal epilepsy	Directed transfer function → Betweenness Centrality (BC)	3–50 Hz	BC changes correlated with the EZ
van Diessen, 2013	12 patients with focal epilepsy (mainly TLE)	Phase lag index → Strength, Eigenvector Centrality (EC)	0.5–50 Hz	Decrease in strength and EC at the theta band, in channels linked with the EZ, compared to the NIZ channels
Goodale, 2020)	15 patients with focal epilepsies (12 with MTLE)	Imaginary coherence → Clustering coefficient (CC), Nodal BC, Strength BC	1–12 Hz (but mainly 4–8 Hz)	Higher values of CC, nodal BC, and strength BC in the EZ & Predictive model using these metrics achieved an accuracy of 80.4% in characterizing the epileptogenicity of an area
		High Frequencies (> 100 Hz)		
Zweiphenning, 2019	18 patients with MCD or tumor	Short-time direct directed transfer function → Strength, Outstrength, Instrength	4–8 Hz, 30–80 Hz, 80–250 Hz, 250–500 Hz	In good outcome patients → Strength and Outstrength in the ripple and gamma bands: Resected tissue > Non-resected tissue
Stergiadis et al. (2023) (Submitted article)	20 patients with neocortical epilepsy	Magnitude squared coherence → BC, CC, EC, Local Efficiency, Local assortativity, strength	80–250 Hz & 250–500 Hz	BC, local efficiency, CC, EC, and strength were significantly correlated with the HFO rates (both ripples and the fast ripples) & Logistic regression models based on these network metrics could define the EZ with accuracies up to 82.5% for ripples and 75.4% for fast ripples

functional network measurements have also been associated with the EZ. Van Diessen et al. used the phase lag index in SEEG data from 12 (mainly TLE) patients, and showed a decrease in strength and eigenvector centrality (EC) at the theta band, in channels linked with the EZ, compared to NIZ channels (van Diessen, 2013). Goodale et al., reported higher clustering coefficient nodal BC, and strength BC in the EZ (Goodale, 2020). After fitting these network measurements in a predictive model they were able to characterize the epileptogenicity of an area with an accuracy of 80.4%. It is however interesting that even in between patients with nearly identical seizure onset areas, the topographic distribution of functional connectivity in the network is unique at the single subject level according to an SEEG study by Marino et al., who used seed-based connectivity (correlation of each electrode with the seizure onset contact) to generate personalized FC networks in 10 focal epilepsy patients (Marino, 2019). Table 2 summarizes the studies where network metrics were used for describing the EZ.

4.2.1. Interictal FC and surgical outcome

Some network measures have also been found to be good predictors of the outcome of surgically treated patients. For example, Shah et al. have demonstrated that, in a linear-correlation-based graphical network, an increased overlap between nodes with high strength values and the resection zone (RZ) was associated with favorable postoperative outcome (Shah, 2019). In another work, that also expanded to some frequencies higher than the conventional (up to 224 Hz), patients characterized by higher global BC values were found to have worse seizure control postoperatively (Grobelny et al., 2018). In this study, it was also demonstrated that the presence of great proportions of high BC nodes was also linked with poor outcomes. This could mean that nodes with high BC values in interictal functional networks could act as regulators that inhibit seizure activity. All studies concerning the usage of interictal FC (direct measurements or networks) in surgical outcome prediction are summarized in Table 3.

All of the aforementioned studies have used a conceptual definition of the EZ, which was mainly defined through iEEG biomarkers and non-invasive neuroimaging. This realization of the EZ comes with the inherent issue of misjudgment of this theoretical area, especially in cases where patients were not seizure-free after surgery. The absence of the ground truth for the EZ can lead to inaccuracies when attempting to study the role of FC in its localization. Thus future works may need to focus on data from good postsurgical outcome patients (ILAE 1, Engel Class I), as in such cases a correct delineation of the EZ is considered. Another way around this problem is the use of the clinically defined RZ, which comes very close to the actual reality of epilepsy surgery (Lagarde et al., 2022). However, this concept comes with several limitations, such as that areas with non-epileptogenic context are included in the RZ (due to purely anatomical reasons), while at the same time, epileptogenic tissue is excluded due to its proximity to the functionally eloquent cortex. A recent advancement towards the objective delineation of the epileptogenic zone has been the EZ fingerprint methodology (Grinenko, 2018; Li et al., 2020). This technique is based on a time-frequency pattern defined by a combination of practical spikes, fast oscillatory activity, and simultaneous suppression of lower frequencies. It has been found that the fingerprint-based EZ.

significantly overlapped with the clinically determined SOZ (71,3% ± 10.2%) (Jiang, 2022).

4.3. Functional connectivity in the high frequency band (> 80 Hz)

Most of the studies discussed so far mainly concerned functional connectivity at a specific subband of the conventional frequency range (0.5–80 Hz). The connectivity of the epileptic brain at the high-frequency band (> 80 Hz) could be of particular interest and potentially provide important insights, as high-frequency activity (HFA) is tightly connected to the epileptogenic process. However, very limited work has been done in this direction.

Table 3

Summary of studies (FC measure level and Network level) that linked interictal FC and surgical outcome in MRE patients.

Authors	Patient population	Connectivity metric	Frequency range	Findings / Main results
			Conventional Frequencies (< 100 Hz)	
Schevon, 2007	9 patients with neocortical epilepsies	Mean phase coherence	0.1–54 Hz & 0.5–65 Hz	Resection of LH regions improves clinical outcome
Ortega et al., 2008	29 patients with TLE	Linear correlation, Mutual information, Phase synchronization	Not mentioned (Nequist frequency = 100 Hz)	No connection between the resection of LH clusters and surgical outcome
Lagarde, 2018	59 patients with focal epilepsy (20 with TLE)	Nonlinear correlation coefficient (h^2)	0.5–80 Hz	Higher values of FC in the NIZ are associated with worse postsurgical outcome
Shah, 2019	27 patients with focal epilepsy (18 with TLE)	Linear correlation	5–15 Hz, 15–25 Hz, 30–40 Hz, 95–105 Hz	Good outcome patients: Higher FC within the EZ compared to patients with bad outcome & Increased overlap between nodes with high strength values and the EZ
Goodale, 2020	15 patients with focal epilepsies (12 with MTLE)	Imaginary coherence	1–12 Hz (but mainly 4–8 Hz)	Good outcome patients present higher FC within the EZ compared to patients with bad outcome
			High Frequencies (> 100 Hz)	
Grobelny et al., 2018	36 patients with focal epilepsy	Granger causality	Exponentially space frequency intervals between 1.5–224 Hz	Higher global BC values associated with worse seizure control postoperatively
Jiang, 2022	27 patients with focal epilepsy (23 with TLE)	Directed transfer function, cross-frequency directionality	1–250 Hz	Higher information flow asymmetry linked with better surgical outcomes & High proportions of high BC nodes linked with poor outcomes
Shen et al., 2023	59 patients with focal epilepsy (24 with TLE)	Time-varying skewness	1–500 Hz	Nodal strength in the skewness-based network can better predict surgical outcome compared to conventional FC measures

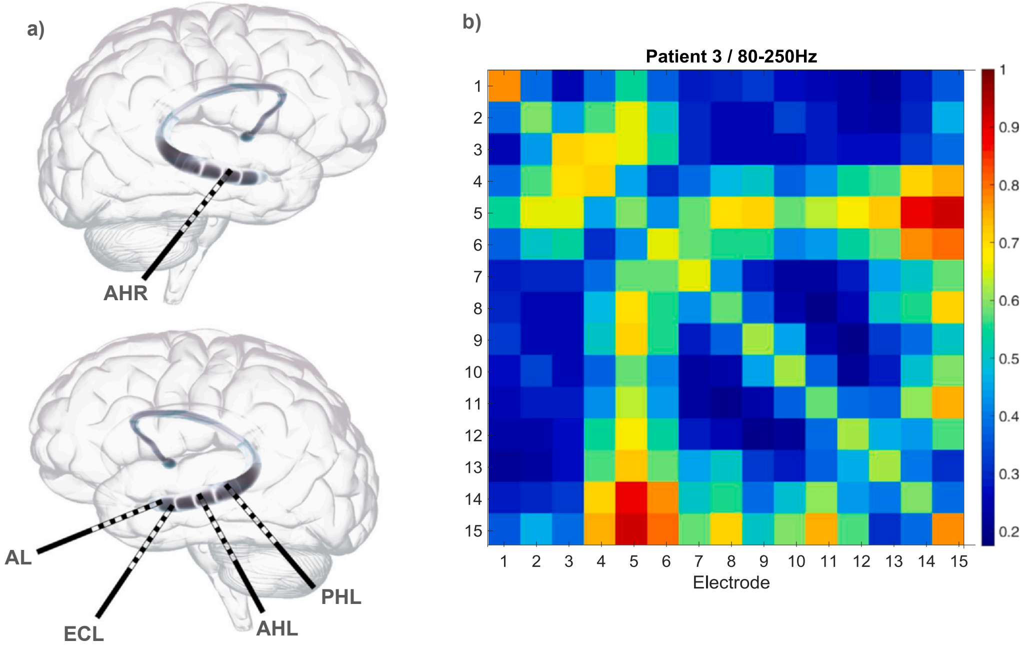

Fig. 3. a) Schematic representation of SEEG electrode placement in a TLE patient (outcome: ILAE1). The electrodes are inserted in temporal areas, and sample the amygdala, the entorhinal cortex, and the hippocampus in both hemispheres b) The adjacency matrix (based on the magnitude squared coherence) of the system in the ripple band (80–250 Hz). Electrode 6 (AHR3–4) has the higher ripple rate, with spatially proximal electrodes 4 (AHR1–2) and 5 (AHR2–3) also presenting high rates. AHR: anterior hippocampus right, AL: amygdala left, ECL: entorhinal cortex left, AHL: anterior hippocampus left, PHL: posterior hippocampus left.

In one of the few studies, (Zweiphenning, 2019) investigated the FC in different frequency bands (theta 4–8 Hz, gamma 30–80 Hz, ripple 80–250 Hz, and fast ripple 250–500 Hz) using the short-time direct directed transfer function (SdDTF), as this specific metric has important methodological advantages, like being robust to noise, performing well in case of non-linear signals (Blinowska, 2011), and being able to correctly identify the underlying structure based on short data segments (Wang et al., 2014). Leveraging the hypothesis that propagating HFOs are the mesoscale representation of the microscale HFO-generating tissue, they hypothesized that studying the functional network in the high-frequency range could help discriminate epileptic from healthy tissue. After interpreting the network, the results showed that in patients with good outcome the tissue that was resected presented a higher total strength and outstrength (sum of all outgoing propagations) in the ripple and gamma bands compared to channels covering non-resected tissue. In addition, channels with interictal events (spikes and HFOs) showed a lower total and instrength (sum of all incoming propagations) and higher outstrength in the fast ripple (FR) band, and a higher total, instrength and outstrength in the gamma band. These results suggest functional isolation of the epileptic tissue in the FR frequency band, and most importantly pinpoint the fact that the total strength in the gamma band seems to be a promising predictor of the epileptic tissue intraoperatively, even when no interictal events (spikes or HFOs) are present in the analyzed segment. This functional isolation of the epileptic tissue confirms and reinforces the results of previous FC works both at the conventional (Lagarde, 2018; Jiang, 2022; Narasimhan, 2020) and the high-frequency range (van Diessen, 2013), (Ibrahim, 2013), (Zweiphenning, 2016), strengthening the idea that functional networks at high frequencies could provide significant value during the presurgical evaluation of patients with MRE.

In another work, Jiang et al. attempted to investigate the information flow (using the directed transfer function and the cross-frequency directionality) between the EZ (defined solely by the SOZ) and the NIZ, in a cohort of 27 focal epilepsy patients (Jiang, 2022). Their results demonstrated a dominant information flow from the NIZ to the EZ across all frequencies, and after a cross-frequency coupling analysis, a general trend of information flow from high frequencies in the NIZ to low frequencies in the EZ.

Along the same line, a very recent study by (Shen et al., 2023) introduced skewness-based functional connectivity (SFC) at the frequency range of HFOs as a method for epileptic tissue localization and surgical outcome evaluation. The idea behind using SFC stems from the realization that direct extension of commonly used FC measurements from conventional frequencies (up to 80 Hz) into the high-frequency band is not informative, due to two major issues: typical HFOs are short-transient events (lasting tens of milliseconds) and their occurrence time and amplitudes are characterized by great variability. As a result, conventional FC measures would capture mostly background activity and not the targeted high-frequency one. In the SFC protocol, time-varying skewness was computed for every channel and then the functional network was constructed based on rank correlation among channels. The connectivity strength in each channel was computed by summing up the edge weights and specific channels were deemed epileptic if they exceeded a certain threshold. The authors proved that SFC achieves better surgical outcome classification, compared to conventional FC in the different frequency bands (from delta to FRs), making it a promising methodology for studying the epileptic network.

We recently reported a study of interictal functional connectivity on a combination of ECoG and SEEG recordings from 20 focal epilepsy patients, using the magnitude squared coherence (MSC) on high-frequencies (80–250 Hz and 250–500 Hz). After interpreting the network with graph theory we found that local graph measures like the betweenness centrality, local efficiency, clustering coefficient, eigenvector centrality, and strength were significantly correlated both with the ripple and the fast ripple rates in the epileptic network (however negatively with the latter). A schematic representation of the electrodes placement and the adjacency matrix in the ripple band for one of the studied patients can be seen in Fig. 3. Interestingly, we also demonstrated that by training a logistic regression model on these local properties of the functional network we were able to predict epileptogenic tissue with an accuracy of 82.5% for ripples and 75.4% for fast ripples. These results highlight the potential of high-frequency functional networks to provide comprehensive information about HFA in patients with MRE, and hopefully pose as a possible future substitute for HFO events themselves (as these come with inherent issues mainly concerning their detection and unpredictability).

5. Conclusion

The studies discussed in this review pinpoint the potential of interictal iEEG-based FC analysis for describing the epileptic process, either by delineating the EZ from non-epileptogenic tissue, or by quantifying the connectivity within and between the EZ, PZ, and NIZ. In the conventional frequency band (0.5–80 Hz), the majority of studies reported that higher values of different connectivity measures were found in electrodes related to the EZ. The EZ was also found to be isolated from the NIZ during the interictal period.

We observed that in more recent works, the generation of a functional graphical network and the interpretation of its different properties (mainly local) for identifying epileptic tissue, is preferred over using the FC measure itself. This trend stems from the need to investigate the importance of hub nodes in the epileptic network, which can be defined by different local properties, and could act as surgical targets for the disconnection of the network. However, contradicting findings in some of the discussed studies complicate hub mapping. Both lower and higher nodal strength values were found to be associated with the EZ. It is important thus to understand that the choice of both the FC measure and the specific frequency band under study can greatly influence the connectivity pattern in epilepsy. Another issue concerns the BC as a metric of hubness of a node, as recent work has shown that the EZ presents high intrinsic connectivity and low connectivity to non epileptogenic regions (Lagarde, 2018). This result suggests that local BC, which is computed by averaging both types of connections, may not be a suitable graphical measure to delineate the EZ. Further studies exploring a range of different local graph parameters (like the clustering coefficient, local assortativity, local efficiency, etc.), in networks constructed with a variety of different FC measures (linear / non-linear, directed / non-directed) could be useful in obtaining a more comprehensive understanding of the underlying organization of epilepsy.

The value of high-frequency activity, and HFOs in particular, in defining areas related to the epileptic process has been increasingly highlighted in the literature of the past decade. However, use of HFOs is still struggling to enter clinical practice. By expanding the FC analysis into the high-frequency band (80–250 Hz) recent works suggest that high-frequency connectivity can predict both the EZ and the surgical outcome in surgically treated MRE patients. However, studying the FC in this band requires specific care, as the connectivity values tend to be lower as frequency rises (Lagarde, 2018) and novel techniques might be needed in order to overcome the issue of "mainly background" activity that is captured at high-frequencies due to the sparseness the of high frequency activity events (Shen et al., 2023). Future work could focus on time-evolving functional networks in the HFO band, in order to monitor the fluctuation of the graph's morphology and the connectivity of the influential nodes across time. Finally, future researchers could also investigate the relationship between FC-based networks and HFO event-based networks, which are generated according to the spatiotemporal propagation of the HFOs in the brain, such as the ones studied by (Tamilia, 2018 ; González Otárula et al., 2019).

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