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REVIEW ARTICLE

High-Frequency Oscillations and Epileptogenic Network

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Abstract: Epilepsy is a network disease caused by aberrant neocortical large-scale connectivity spanning regions on the scale of several centimeters. High-frequency oscillations, characterized by the 80-600 Hz signals in electroencephalography, have been proven to be a promising biomarker of epilepsy that can be used in assessing the severity and susceptibility of epilepsy as well as the location of the epileptogenic zone. However, the presence of a high-frequency oscillation network remains a topic of debate as high-frequency oscillations have been previously thought to be incapable of propagation, and the relationship between high-frequency oscillations and the epileptogenic network has rarely been discussed. Some recent studies reported that high-frequency oscillations may behave like networks that are closely relevant to the epileptogenic network. Pathological high-frequency oscillations are network-driven phenomena and elucidate epileptogenic network development; high-frequency oscillations show different characteristics coincident with the epileptogenic network dynamics, and cross-frequency coupling between high-frequency oscillations and other signals may mediate the generation and propagation of abnormal discharges across the network.

Keywords: High-frequency oscillations, HFO network, epileptogenic network, biomarker in epilepsy, epileptogenic zone, surgery.

1. INTRODUCTION

For patients with medically refractory epilepsy, surgical removal of the epileptogenic zone (EZ) is the most promising approach. This method is based on the traditional focal-onset hypothesis [1]. However, tailoring surgery is not always effective despite complete removal of the putative seizure source [2], and some rapid seizures often spread across large brain areas [3]. The past decade has seen an increasing consensus over the idea that epilepsy should be considered a network disease caused by coordinated activity across large-scale anatomical structures or functional connections of different brain regions [4-10]. The concept of an epileptogenic network has been proven by many methods, such as functional magnetic resonance imaging (fMRI) [11-13], diffusion tensor imaging (DTI) [14, 15], and computational models [16, 17]. Through high-resolution mapping of biomarkers of epileptogenicity, electroencephalography (EEG), in particular intracranial electroencephalography (iEEG), allows for direct visualization of the epileptogenic network and its dynamic evolution in time [18-20].

High-frequency oscillations (HFOs) have been thought to be a promising biomarker of epileptogenicity [21-25]. HFOs are spontaneous EEG events in the frequency range between 80 and 600 Hz that consist of at least four clearly identifiable oscillations from the background activity [23]. HFOs can be further divided into ripples (80-200 Hz/80-250 Hz) and fast ripples (FRs, 200-500 Hz/250-600 Hz). They are believed to participate in the overall epilepsy pathological process, including both seizure generation and propagation. High-rate HFOs are often found in the seizure onset zone (SOZ) and EZ, and removal of areas generating high-rate HFOs tends to yield better outcomes [26-28]. Due to the limited generating volume of HFOs, it was previously believed that HFOs could not propagate, limiting the discussion of the relationships between HFOs and the epileptogenic network [29]. The latest studies, however, have begun to overturn previous beliefs and attempted to explore the HFO-related network and its correlation with the epileptogenic network [30]. Since HFOs are generated by local neuronal circuits, evaluations of HFOs and HFO-involved networks can partially reveal the epileptogenic network on the microscale neuronal circuitry level and possibly inspire novel treatment methods [31].

In this review, we discuss the existence of the HFO network and examine the relationship between HFOs and the epileptogenic network, especially focusing on the roles of HFOs in epileptogenic network formation; the evolution of HFO characteristics during epileptogenic network dynamics, including the interictal, ictal, and post-treatment phases; and the cross-frequency coupling of HFOs and other signals in the multiscale network interface. Based on these descrip-

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tions, we explore the directions and challenges of HFOs' application in the future diagnosis and treatment of epilepsy.

2. WHAT IS AN EPILEPTOGENIC NETWORK?

Epileptogenic networks are defined as the brain regions involved in the production and propagation of epileptic activities [32]. The network concept has been proposed as a key factor in identifying the anatomical distribution of the epileptogenic process, as well as offering a framework to describe the dynamic course of seizures and their clinical expression. However, the concept of an epileptogenic network concept is fundamentally metaphorical since there is no corresponding physical entity, and the definition of these networks is also largely dependent on the methodologic approaches. Thus, as with any new field, the best practices for constructing and analyzing brain networks are still evolving.

In neuroimaging data, network nodes are almost always parcels of gray matter voxels that are used to analyze the structural connectivity (SC) networks referred to nodes linked by physical connections and functional connectivity (FC) networks of the strength of the statistical relationship between nodes' activity over time [33, 34]. The SC networks show an extension of cortical abnormalities outside the EZ, as measured by cortical thickness or volumetry [35], while the FC networks reveal connectivity changes within regions affected by seizures [36]. Since epilepsies are characterized by altered brain rhythms, studies based on EEG recording are crucial [32]. The spreading of abnormal discharges over time in EEG recordings has been shown to be consistent with the evolution of clinical symptoms, and epileptogenic networks can be related to structures quite distant from the lesion and even separate from the region of maximal interictal spiking [32]. These studies on epileptogenic networks are dependent on neuroimaging and EEG recordings as well as clinical manifestation to understand the epileptogenic network on a large scale.

In 2017, the International League Against Epilepsy Workshop on Neurobiology of Epilepsy proposed that the epileptogenic network is a multiscale hierarchical organization [37], *i.e.*, epilepsy is a disease of different network hierarchies that range from genes to clinical phenotypes: gene expression is required for protein production, which is needed for cell signaling, which facilitates transmission across a synapse, formation of microcircuits, and so on up to affecting the whole-brain that lead to the emergence of seizures as a symptom [31]. Among these hierarchies, the cellular-level activity affects local circuits at the level of neurons and synapses and may be measured as local field potentials, like HFOs. The multiscale network concept suggests that our understanding of the epileptogenic network needs to focus on the large as well as the small scale. Stam *et al.* reported that 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) [38]. Therefore, HFO analysis, which studies the multiscale epileptogenic network at the local neuronal circuitry level, can improve our understanding of epileptogenic networks (Fig. **1**) [31]. Thus, a discussion of HFOs is of great theoretical and clinical significance for the concept of epileptogenic networks.

3. DOES THE HFO NETWORK EXIST?

HFOs have long been considered to reflect the pathological activities of the epileptogenic network because they are closely related to the hyperexcitability of brain tissues. However, it is debatable whether HFOs, especially the FRs, are involved in the formation of epileptic networks or are simply a byproduct of these networks. In the past, HFOs were believed to originate from very limited areas without the ability to propagate [39]. However, this view is limited for the following reasons: 1) HFO recordings were usually based on intracranial macroelectrodes, which capture signals from areas too big to explore small-scale HFO propagation; 2) due to the limited number of implanted intracranial electrodes, the areas actually recorded were limited, increasing the probability of missing HFO propagation in certain areas; 3) HFO analysis usually depended on static and individual analyses rather than dynamic and multimodal comparisons. The development of recording technologies like microelectrodes, magnetoencephalogram (MEG), high-density scalp EEG, and EEG-functional MRI (EEG-fMRI), as well as advanced analytical methods such as multimodal analysis and network computing, has contributed to HFO research [40]. With the help of these advanced technologies, an increasing number of studies have started to address the possibility of HFO propagation. Ortiz *et al.* used a matrix of 4096 microelectrodes to focus on different subregions of the hippocampus in the entorhinal cortex-hippocampus slices of rats, and found that FRs were generated in CA3 and spread from CA3 to the hilum and dentate gyrus [41]. Korzeniewska *et al.* found that in patients with medically resistant partial-onset seizures, propagation of ripples was mostly centered at sites identified as part of the ictal onset, while little propagation was observed among other sites [42]. Zijlmans' group reported that partial removal of the FR-producing brain regions detected by electrocorticography (ECoG) during surgery resulted in favorable surgical outcomes as long as FRs disappeared from the non-removed brain regions [43, 44]. These spatiotemporal distribution changes of HFOs demonstrated the existence of HFO propagation and its related networks. However, due to the differences in mapping algorithms, the HFO networks outlined by different groups may vary. Zijlmans *et al.* mapped the FR band network using phase lag index (PLI) values and found a functional integration in the FR band network of channels covering presumed epileptogenic tissue [39, 45]. Gotman's group mapped the HFO network based on a temporal order in patients with focal epilepsy and found that the ripple network appeared to be larger than the fast ripple network. They also calculated the median propagation speeds of different bands on the basis of Euclidean distances and reported speeds of 0.74 mm/ms for ripples and 1.75 mm/ms for FRs [30]. Thus, considering their limited generation and propagation volume, HFO networks are focal but include the SOZ and early diffusion regions.

HFO networks are dynamic, consistent with epileptogenic network dynamics. The characteristics and regional involvement of HFO networks differ based on the recording and analysis methods: feature analysis may show the variations in rates, power, and other features with temporal and spatial variations, while network calculations can reveal the connectional and functional changes. Therefore, in the

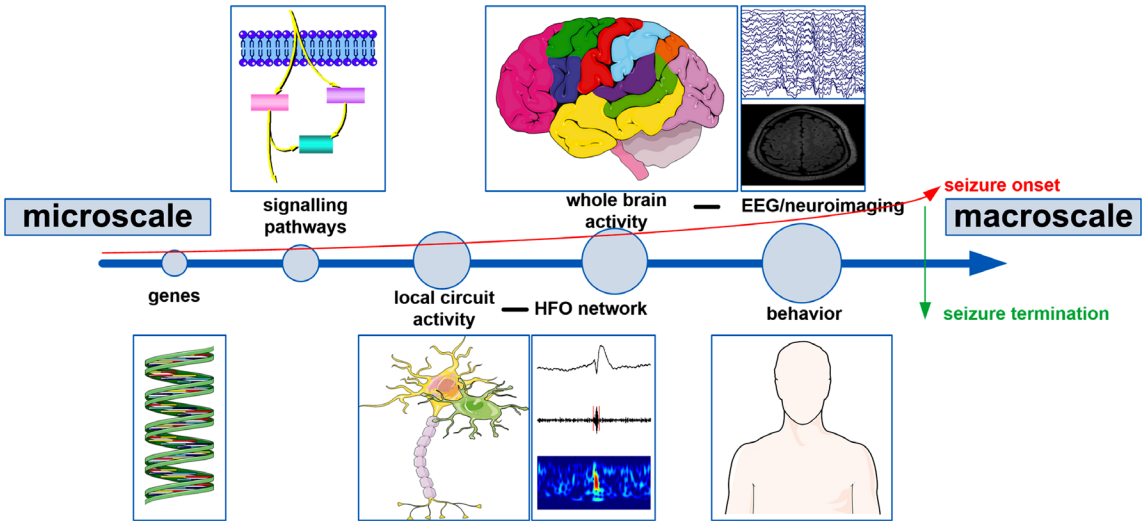

Fig. (1). The multiscale/hierarchical epileptogenic network. From microscale to macroscale, the network involves genes, signaling pathways, local circuits, and then manifests as whole-brain activity and behaviors. When the excitabilities of the network increases, the seizures starts and reduced excitabilities lead to seizure termination. *(A higher resolution/colour version of this figure is available in the electronic copy of the article).*

following section, we will discuss the HFO network's relationship with the epileptogenic network on the basis of feature and connection changes.

4. RELATIONSHIP BETWEEN THE HFO/HFO NETWORK AND THE EPILEPTOGENIC NETWORK

4.1. HFOs' Emergence Reveals the Formation of the Epileptogenic Network

Since HFO rates vary within the same areas marked by a macroscale network, a detailed microscale understanding of seizure mechanisms, encompassing cellular signaling and communication, is key to investigate the differences in macroscopic epilepsy expression [46]. Here, we would like to address the relevance of this micro-macro interaction in the epileptogenic network.

Epileptogenic networks are believed to be the result of recurrent and hypersynchronous runaway excitations across multiple scales [46]. At the microscopic level, the network presents as abnormal neuron discharges and fast recruitment of pathologically interconnected cells through gap junctions, ephaptic interactions, and changes in the concentrations of extracellular ions (*e.g.*, K^+). HFOs are generated by these local overexcitation networks, especially through the activities of pyramidal cells and interneurons [47-50]. The different neuronal networks give rise to specific types of HFO bands [51, 52]. For instance, pathological ripples are associated with the interneuron network [53, 54]. Ripples reflected summed inhibitory postsynaptic potentials in pyramidal cells as a result of high frequency barrage of interneurons [53]. Meanwhile, FRs are derived from the principal cell network [54-57]. FRs may reflect the pathological hypersynchronous population spikes of bursting pyramidal cells [56]. Considering that its high frequency is beyond the physiologic limits of neuronal firing, FRs may be relevant to the out-of-phase firing of different subpopulations of synchronized neurons as characterized by reduced spike time variability, uncorrelated firing, delayed activation, disconnected neural populations, or complex network connectivity patterns with a high level of clustering due to the presence of hub neurons. Furthermore, GABAergic interneurons may also play an active role in the generation of pathological FRs by promoting neuronal network synchrony in pediatric epilepsy patients [58-60]. In an underdeveloped immature brain, FR generation is commonly related to malfunctioning GABAergic interneurons. A possible explanation for such a unique phenomenon is that the accumulation of Cl- inside interneurons due to the expression of a type of the Na^+-K^+-$2Cl^+$ cotransporter NKCC1 would result in a depolarizing Ecl and thereby cause excitatory current flow during GABA receptor activation [61]. Although the levels of NKCC1 reduce as the brain becomes fully developed, the pathologically excitatory GABAergic current also takes place when KCC2, another K^+-Cl^+ cotransporter, is downregulated under some pathophysiological conditions [61, 62]. Pallud *et al.* found that peritumoral neocortex infiltrated by glioma cells generates spontaneous epileptic discharges depending on both AMPA glutamatergic and GABAergic signaling, which indicates a reduced KCC2 and increased NKCC1 expression [63]. The efficacy of benzodiazepines, which act as positive modulators of chloride permeable GABAA receptors, dramatically decreases with increasing durations of status epilepticus (SE), with the hypothesis that excitatory GABAergic signaling is associated with benzodiazepine resistance in SE [64, 65]. In the long term, this would alter the synaptic plasticity, thus establishing the epileptogenic network. This process further exacerbates the emergence and increase in HFOs [61]. Since HFOs arise from these pathologically excitatory neuron firings and firing synchronizations, HFO features and networks would be expected to mirror the microscale network during the course of epileptogenesis.

As an indicator of epileptogenic network formation, HFOs could be used as a marker for seizure potentiality evaluation. In the intrahippocampal kainite-induced epilepsy rat model, all rats with HFO activities experienced recurrent spontaneous seizures later, whereas none of the rats without

HFOs developed seizures [66]. After SE induced by kainic acid injection into CA3, rats showed spontaneous seizures along with high-frequency activities like bursts of population spikes (BPS) in CA1 and dentate gyrus as well as pathological HFOs (pHFOs) in the perilesion [67]. The HFOs of 60-120 Hz are thought to refer to the development of a secondary mirror focus since researchers found that the spontaneous seizures developed in the naive non-kainate-treated contralateral side where HFOs (60-120 Hz) were generated from [68]. In 2019, a multi-center study also highlighted that HFOs reflect progressive neuronal disturbances after an epileptogenic brain injury and serve as a biomarker of post-traumatic epilepsy (PTE) [69]. In contrast, since HFOs are related to the microscale network and clinical seizures originate from the macroscale network, their time delays need to be further measured.

4.2. The HFOs and HFO Network Change with Epileptogenic Network Dynamics

Epileptogenic networks encompass three temporal stages, namely, interictal, preictal, and ictal [70]. The HFOs and HFO networks show changes with the epileptogenic network dynamics. Thus, investigation of the evolution of HFOs or HFO networks over time can provide insights into the dynamics of the epileptogenic network as it evolves (Table **1**).

4.2.1. Interictal Period

Sleep and wake states have been found to play a role in epileptogenic network regulation. Non-rapid eye movement (NREM) sleep facilitates epileptogenic networks, while rapid eye movement (REM) sleep suppresses them [71]. On the other hand, normal physiological functions during wakefulness can conceal the presence of these networks. As a result, there are fewer HFOs in the awake and REM epochs than during NREM [72-74]. The number of abnormal discharges as well as their propagation increase during NREM sleep, which can reveal the epileptogenic network that is hidden during wakefulness [71]. It was proposed that the epileptogenic network hijacks and transforms the physiological neural network during the derailment of NREM sleep homeostasis. Such a sleep-related seizure origin helps explain the concurrence of epileptiform HFOs and slow waves and spindles in NREM sleep [75]. Although the repetition rate and propagation network of HFOs increase during NREM sleep, their basic localization and morphology are always preserved maximally within the EZ, especially for FRs [72, 73]. Therefore, observation of the interictal HFO distribution and exploration of related networks may serve as a window for understanding the epileptogenic network better and finding the essential nodes in the network. Effective connectivity (EC) neural network analysis showed that patients with insular epilepsy display alterations in the interictal HFO network involved in both whole-brain connectivity and the insula-based network [76]. Interictal high rates of ripples seem to be associated with a more active pathologic cortical-thalamocortical network, which is consistent with the blood-oxygen-level-dependent (BOLD) signals [77]. However, whether short-segment HFO analysis is sufficient to characterize the epileptogenic network fully is still debatable. In 2018, Gliske *et al.* found that the localization of the strongest HFO varied over time in each epoch, and some variations in HFOs could be traced back to variations in the epileptogenic networks. Thus, a robust interpretation of HFOs must discuss its interaction with epileptogenic networks and analyze the complete clinical data instead of short data segments [78] .

4.2.2. Ictal Period

During the interictal to ictal state evolution, Granger causality results based on the directionality and intensity of high-frequency activity (70-175 Hz) propagation show prominent transformation from divergence to convergence at the ictal onset zone [42]. Much before the seizure onset, HFOs increase [79, 80], and Epstein *et al.* mapped the preictal high-frequency network activity by Granger causality analysis that appears to show up earlier and cover an extensive area [81]. These studies demonstrate that the macroscale network shown through EEG abnormalities or clinical symptoms is preceded by the activation of a microscale network (like the HFO network) based on neuronal circuits. Since HFOs could represent these early microcircuit defections, they may help elucidate the mechanisms underlying ictogenesis and predict seizures.

At the seizure onset, HFOs increase greatly and are largely localized in the seizure focus [82], which implies that the seizure focus plays a central role in the ictal epileptogenic network. Fisher *et al.* also found, in this moment, that the majority of nodes in the HFO network were connected to a single dominant component and that the percentage of nodes within the largest component grew significantly [82]. In the generation of epileptic spasms (ES), ictal HFOs revealed a network consisting of multilobar cortical regions (frontal, parietal, and temporal), but sparing the positive motor area [83]. At the beginning of temporal lobe epilepsy (TLE), different types of seizure onset activate distinct neuronal networks. Analogously, discrete alterations were presented by each type of HFO band. Characterized by an onset pattern of 2 Hz focal spiking and mainly associated with FRs, hypersynchronous-onset (HYP) seizures are involved with interneuron (inhibitory) networks [84]; in contrast, low-voltage-fast onset (LVF) seizures, which are characterized by an initial, isolated spike followed by low-amplitude fast activity, present with a predominance of ripples and activate principal (glutamatergic) networks [85-87].

As the seizure progress, the functional connection of the FR band within epileptic tissue increases [58], and HFO propagation corresponds to the ictal semiology, revealing the epileptogenic network involved in seizure initiation and progression [88]. Recently, a study based on focal seizures, either with or without secondary generalization, showed that numerous within- and cross-frequency (low- and high-frequency activities or low-to-high cross-frequency coupling) push-pull dynamics regulate seizure propagation, potentially reflecting impaired excitation-inhibition interactions of the epileptogenic network [17].

After seizures, the spike number increases, whereas the HFO rates remain the same or decrease to the level in interperiods [89, 90]. Postictal HFO decrease might reflect postictal inhibition of the epileptogenic network [90], suggesting that, compared with spikes, HFOs are more consistent with epileptogenic network status changes.

Table 1. HFOs dynamics correspond to epileptogenic network.

Period	References	Model	Data/Band	Finding	Significance
Latency	-				
	Bragin *et al.* [66]	Rats (chronic, KA-induced seizure)	3 - 5 min SWS/R (100-200Hz); FR (200-500Hz)	Correlation between detection of HFOs and spontaneous seizures	HFOs' role in the process of epileptogenesis.
	Bragin *et al.* [67]	Rats (chronic, KA-induced seizure)	SWS/R(80-200Hz); gamma(40-80Hz)	Rats that later developed seizures of a new pattern consisting BPS.	BPS as a primary consequence of SE with progressive epileptogenesis.
	Santana-Gomez *et al.* [69]	Rats (after a TBI)	10 min SWS/HFO (80-500Hz)	EEG files from 2 of 3 centers contained bursts of HFOs.	HFOs as a biomarker of PTE.
Ictal	-				
pre-Ictal	Worrell *et al.* [79]	Patients (neocortical epilepsy)	2 h seizure EEG containing the seizure onset at 1 h and 50 min/ R (60-100Hz)	High-frequency activity increased mostly in the 20 min prior to neocortical seizure onset.	HFOs' role in neocortical ictogenesis, predict seizure and locate SOZ.
	Epstein *et al.* [81]	Patients (intractable epilepsy)	Whole iEEG/-250Hz; -500Hz	Widespread preictal 80-250Hz GC network began 2 - 42 s before visible electrographic onset	HFOs' role in seizure genesis
Seizure start	Fisher *et al.* [82]	Patients (intractable epilepsy)	4 min prior to and 2 min /0.1-300Hz	(1) Large increase in the 80-120 Hz portion at seizure start. (2) HFOs increased were mostly in the seizure focus.	HFOs may locate seizure focus.
	Le´vesque *et al.* [84]	Rats (chronic, pilocarpine-induced seizure)	Whole records/R (80-200Hz); FR (250-500Hz)	Ripples predominate during LVF seizures and fast ripples during HYP seizures.	R and FR may have different roles in ictogenesis.
	Schonberger *et al.* [87]	Patients (MTLE with HYP/LVF onset)	Two 5 s intervals (pre-ictal; initial ictal)/R (80-250Hz); FR (>250Hz)	(1) Pre-ictal/ initial ictal fast ripple density and rate were higher for HYP than LVF onset. (2) Fast ripple density\rate\amplitude and ripple amplitude were higher in LVF after HYP than during LVF without preceding HYP.	(1) FR may contribute generation of HYP seizure. (2) FR may facilitate classification.
Seizure evolution	Avoli *et al.* [85]	Rats (acute, 4-AP induced seizure)	500 s before the onset and to 300 s after each seizure/R (80-200Hz); FR (250-500Hz)	Fast ripples of the SE group occurred at higher rates than ripples.	FRs may pinpoint seizures progressing to SE.
	Akiyama *et al.* [88]	Patients (intractable Jacksonian epilepsy)	Interictal (baseline) and ictal video-EEG excerpts/40 - 80, 80 - 200, and 200 - 300 Hz frequency bands	(1) Ictal HFO propagation corresponding to the ictal semiology in Jacksonian seizures. (2) Ictal HFOs limited. (3) During seizure initiation, HFO amplitude were higher.	HFOs' role in epileptic network involved in seizure initiation and progression.
	Tenney *et al.* [168]	Patients (with untreated childhood absence seizures)	1 minute before seizure to 1 minute after seizure (EEG; MEG)/1-20, 20-70, and 70-150Hz bandwidths	Cortical sources of HFO bandwidth (70-150Hz) localized primarily to the frontal region.	Co-occurring frontal and parietal corticothalamic networks may interact to the generation of discharges.

(Table 1) contd….

Period	References	Model	Data/Band	Finding	Significance
-	Korzeniewska *et al.* [42]	Patients (intractable epilepsy)	Ictal, preictal and interictal intervals/high frequency activity (70 - 175 Hz)	The focal ictal onset zone had prominent divergence and convergence of high frequency activity propagation.	HFO network during seizure may help locating SOZ.
	Jiang *et al.* [17]	Patients (focal seizures; secondary generalization)	Preictal, ictal, and postictal / 1-4,4-8,8-13,13-30,30-80,80-150Hz	The secondary generalization of focal seizures is regulated by numerous within- and cross-frequency push-pull dynamics	Impaired excitation-inhibition interactions of the epileptic network.
	Fujiwara *et al.* [169]	Patients (intractable epilepsy)	Seizure epoch/ 80 - 150, 150 - 300, and 300 - 500 Hz	Complete resection of ictal HFOs lead to good outcome.	Complete removing HFOs could predict surgical outcome.
post-Ictal	Zijlmans *et al.* [89]	Patients (intractable epilepsy)	1 min SWS per night; 5 - 8 night/R (80 - 250Hz); FR (250 - 500Hz)	After seizures, there was an increase in spikes, whereas HFO rates remained the same.	HFOs' role in seizure genesis.
	Nadja *et al.* [90]	Rats (chronic, KA-induced seizure)	Preictal, ictal, and postictal/ R (80-250Hz); FR (250-500Hz)	HFOs significantly decreased during postictal periods compared to the ictal segment.	Postictal HFO decrease might reflect postictal inhibition of epileptic activity.
Interictal	-				
	Staba *et al.* [72]	Patients (intractable epilepsy)	Sleep epoch between 10 PM to 7 AM/ R (80 - 200Hz); FR (200 - 500Hz)	(1) Compared to R, FRs rates were higher in EZ (2) HFOs showed highest rates during SWS. (3) During REM, R were lowest, FRs remained elevated	FRs were related to seizure-generating areas.
	Worrell *et al.* [79]	Patients (neocortical epilepsy)	15 min SWS and wake baseline records/R (60-100Hz)	High-frequency activity rates were maximal during SWS.	Explain the propensity for neocortical onset seizures to begin during sleep.
	Yin *et al.* [76]	Patients (insula epilepsy); healthy control	MEG data/R(80-250Hz)	Alterations of the interictal HFO networks.	The dysfunction of HFO networks as a novel biomarker in insular epilepsy.
	Fahoum *et al.* [77]	Patients (focal epilepsy)	30 min SWS/ 40-80Hz; >80Hz	Scalp IEDs accompanied by HFOs are associated with larger metabolic responses and with thalamic involvement lateralized to the side of cortical ripples.	Ripples is associated with a highly-active cortical-thalamo-cortical network.
	Gliske *et al.* [78]	Patients (intractable epilepsy); healthy control	10-min sleep segments /80-500Hz; 200-500Hz	The precise localization of different epochs is consistent in only 22% of patients.	HFOs analysis requires prolonged EEG data and other clinical data.
ASMs	-				
	Zijlmans *et al.* [89]	Patients (intractable epilepsy)	1 min SWS per night;5-8 night/R (80-250Hz); FR (250-500Hz)	Medication reduction induced an increase in HFO rates and mean duration.	HFOs may be a biomarker for epilepsy activity.
	Kramer *et al.* [100]	Patients (children with BECTS); healthy control	15 min SWS/R(100-300Hz)	Scalp ripple rate was higher in subjects with active epilepsy /who were seizure-free ON medication.	Scalp ripples are a specific non-invasive biomarker for seizure risk.

(Table 1) contd….

Period	Reference	Model	Data/Band	Finding	Significance
	Le´vesque *et al.* [92]	Rats (chronic, pilocarpine-induced seizure)	Whole EEG/ R (80-200Hz); FR (250-500Hz)	LEV-treated animals without seizures had lower HFO rates.	HFOs may mirror anti-ictogenic properties of LEV.
	Herrington *et al.* [93]	Brain slices (4-AP-induced discharge)	Field potential recordings/ R (80-200Hz); FR (250-500Hz)	THDOC reduced HFOs.	THDOC may modulate epileptiform synchronization by potentiating $GABA_A$ receptor-mediated signaling (revealed by HFOs)
	Cao *et al.* [99]	Patients (children with CSWS)	First 3 min SWS/HFO (80-500Hz)	HFO rates were higher in the response with relapse group.	Interictal scalp HFOs may predict seizure and cognitive. outcome in CSWS
	Yan *et al.* [97]	Patients (children with IS); healthy control	5 min sleep or awake stage/ HFO (80-300Hz), gamma, ripple, and FR band	The average HFO energy of the effective group was lower than that of the ineffective group in the sleep stage.	The analysis of average HFO energy can be used as a predictor of the effectiveness of epilepsy treatment.
	Wang *et al.* [98]	Patients (children with IS)	5 min SWS/R (80-200Hz)	(1) After ACTH treatment, the percentage decrease in the number, spectral power, and channels of ripples was significantly higher in the seizure-free group. (2) The relapse subgroup showed higher number and spectral power and wider distribution of ripples.	Scalp HFOs can be used as an effective biomarker to monitor the effect and evaluate the prognosis of ACTH therapy in patients with IS.
Surgery	-				
ECoG	Wu *et al.* [170]	Patients (children, intractable epilepsy)	ECoG recording/FR (250-500Hz)	Complete resection of FRs cortex correlated with postoperative seizure freedom.	FRs could be recorded in ECoG and guide surgical resection.
	Van Klink *et al.* [43]	Patients (intractable epilepsy)	1minute intra-operative ECoG/ R (80-250Hz); FR (250-500Hz); spike	(1) HFO and spike rates decreased after resection. (2) Post-ECoG FRs occurred one poor-outcome patient. (3) Post-ECoG R not on spike were more in good-outcome patient	(1) ECoG FRs could help locate EZ. (2) ECoG R may be physiological. (3) Post-ECoG HFOs may predict outcome
	van 't Klooster *et al.* [102]	Patients (intractable epilepsy)	1minute pre and post ECoG / R (80-250Hz); FR (250-500Hz); spike	The percentage of resected FRs, ripples, or spikes in pre-ECoG could not predicted outcome but post-ECoG FRs could.	Post-ECoG FRs predicted outcome.
SEEG	Scholly *et al.* [101]	Patient (one, PNH-related intractable epilepsy)	5 min SWS/ R (80-250Hz); FR (250-330Hz)	The running down ofc HFO and spikes following thermocoagulations correlated with seizure control.	HFOs help to evaluate the disease activity.

Abbreviations: KA, kainic acid; SWS, slow-wave sleep; R, ripple; FR, fast ripple; HFO, High-frequency oscillations; BPS, bursts of population spikes; SE, status epilepticus; TBI, traumatic brain injury; PTE, post-traumatic epilepsy; EEG, electroencephalogram; iEEG, intracranial electroencephalogram; GC, Granger causality; SOZ, seizure onset zone; LVF, Low-voltage-fast onset; HYP, hypersynchronous onset; MTLE, medial temporal lobe epilepsy; 4-AP, 4-aminopyridine; MEG, magnetoencephalogram; EZ, epileptogenic zone; REM, rapid eye movement; IEDs, interictal epileptiform spikes; BECT, benign epilepsy with centro-temporal spikes; LEV, levetiracetam; THDOC, allotetrahydrodeoxycorticosterone; IS, infantile spasms; ACTH, adrenocorticotropic hormone; GABA, gamma-aminobutyric acid; CSWS, continuous spike-and-wave during sleep; ECoG, electrocorticogram; PNH, periventricular nodular heterotopia.

4.3. HFO/HFO Network Changes can be Used to Monitor Epileptogenic Network Changes Post-treatment

4.3.1. Post-medication

Since the HFO/HFO network mirrors the excitability of the epileptogenic network, the HFO changes after drug therapy may indicate changes in the epileptogenic network state, such as upturns and relapses. Etomidate administration can activate the HFO network and significantly increase HFO rates, but the activation is limited to the SOZ and the areas removed during surgery, which is consistent with the epileptogenic network [91]. In both animal models and patients, the seizure reduction after anti-seizure medication (ASM) treatment is related to an HFO decrease [92-98]. In contrast, the relapse group always showed significantly higher persistent HFOs [99]. Moreover, medication reduction is followed

by an increase in HFO rates and mean duration [89]. In 2019, Kramer *et al.* found that scalp spike ripples decreased greatly in patients achieving seizure-free status in comparison with those showing recurrent seizures after receiving medication. They concluded that spike ripples are a specific non-invasive biomarker for recurrent seizure risk and guiding medication trials [100].

4.3.2. Post-surgery

As shown on ECoG, while HFO rates decrease after surgical resection of epileptogenic tissue, ripples of isolated spikes (may be physiological) increase in sensorimotor areas [43]. The running down of interictal HFOs and spikes in heterotopic and normotopic sites involved at the seizure onset following radiofrequency thermocoagulation (RF-TC) shows a good correlation with significantly improved seizure control [101]. These results indicate that the disappearance of pHFOs and the appearance of physiological rhythms can reveal HFO network changes and further indicate the abruption of the epileptogenic network as well as the recovery of the physiological brain circuit. Interestingly, in some patients, new FRs appear in the postoperative ECoG from the near or remote areas to the resection and predict poor postsurgical outcomes [102]. The emerging FRs suggest that once the strongest discharge nodes are wiped out, the surrounding nodes may take over as a new epileptogenic center in the epileptogenic network [46].

5. HFO CROSS-FREQUENCY INTERPLAY MEDIATES THE EPILEPTOGENIC NETWORK

Small-scale neuronal networks may impose widespread effects on the overall epileptogenic network dynamics, with signal interactions existing on a multiscale basis. Cross-frequency interplays such as cross-frequency coupling (CFC) and cooccurrence degree differ in individual brain areas [103]. Specifically, stronger interplays always appear in the core in comparison with the penumbra territories of the network. This interplay mediates the spread of seizures across the surrounding macroscopic network [104], showing decreasing strength as the seizure develops. Since different frequencies arise from different neuronal activities and environmental mediation, an exploration of CFC and cooccurrence may provide insights into the seizure genesis mechanisms and the distinction between the core and penumbra territories of the epileptogenic network.

5.1. HFOs and the Direct Current Shift

Direct current shifts (DC shifts) are ictal baseline shifts occurring at very a low frequency (0.016-1 Hz) recorded by the DC amplifier, although researchers like Ikeda *et al.* and Rodin *et al.* reported that such activities could also be detected by an AC amplifier with a long time constant [105, 106]. DC shifts are believed to arise from glia cells, neuron-glia interactions, or the brain/CSF-blood interface [107, 108]. The coexistence and coupling of DC shifts and HFOs are believed to be related to seizure generation [109, 110], suggesting a complex interplay between the neurons and the surrounding milieu as part of the epileptogenic network. DC shifts and HFOs occur earlier than the findings demonstrated on conventional ictal EEG. A few minutes before the seizures, strong phase-amplitude coupling of DC shifts and HFOs already manifests as a surge and is followed by strong discharges of ictal HFOs. This early surge could represent a neural process for the preparation of ictal HFO discharges, indicating a potential role of glia cells in the excitation and synchronization processes across the epileptogenic network. This phenomenon also makes it a potential reference for seizure prediction [111-113]. Some articles have also reported the temporal cooccurrence and partial spatial overlap of DC shifts and ictal HFOs. This temporal and spatial interplay, which implies high local excitability, is commonly observed in confined areas concordant with the ictal onset zone but not the irritative zone. Thus, through the detection of DC shifts and HFO interplay, the core of epilepsy-generating tissues in the epileptogenic network can be delineated [108, 112-117]. These overlapping waveforms, also called "red slow," significantly decrease after seizures [118].

5.2. HFOs & Low-frequency Rhythms

The phase of low-frequency rhythms has been reported to modulate the amplitude of high-frequency activity [119]. As reported, low-frequency signals are formed by a large-scale cellular network, while high-frequency rhythms are formed by a small-scale network [120]. Together, their CFCs may pinpoint multiscale network interactions. CFCs are significantly elevated in the SOZ and EZ in comparison with the non-epileptic regions and thus may serve as an alternative measure for recruiting highly excited local areas through the detection of ictal activities [121-124]. In addition, physiological and epileptic HFOs seem to have different CFC features, indicating the distinction between the physiological network and the epileptogenic network [125]. Jacobs *et al.* thought that physiological HFOs occur at the trough of low-frequency (4-8 Hz) phases [126]. Frauscher *et al.* showed that epileptic HFOs in the EZ predominated during the transition from the "up" to the "down" state of slow waves (0.3-4 Hz), while physiological EEG rhythms were activated by the "up" state [125]. Ren *et al.* found that ripples in the EZ tended to be closer to the down-state peak of the slow wave (0.1-4 Hz) and had a steeper slope/wider distribution ratio than those in the non-EZ [127].

The cross-frequency amplitude-to-phase couplings are consistent with the epileptogenic network ictal status changes, including the initiation, spread, and termination of seizures. In general, alpha oscillations reflect fundamental mechanisms of cortical inhibition and idling that may direct information flow within brain networks across different contexts [128] and show strong CFCs with physiological HFOs [126]. However, at seizure initiation, CFCs between high- and low-frequency (theta and alpha, 6-14 Hz) oscillations become largely inconsistent. This disruption of normal CFC relationships may reflect the breakdown of inhibitory processes regulating functional segregation and integration in epileptogenic networks, which would further lead to seizure onset [122]. During seizure development, the phase-amplitude coupling of FRs and 3-5 Hz slow waves was synchronized, propagating the activity across large-scale epileptogenic networks. Therefore, CFCs could have been the fundamental mechanism underlying the spread of epileptic activities in macroscale [123, 129]. At the point of seizure termination, normal oscillatory activity and FC recovered within the epileptogenic network along with reappearance of strong normal CFC [122].

Additionally, HFO occurrence was shown to occur during different phases of the slow-frequency oscillations in LVF and low-frequency high-amplitude periodic spiking (PS) seizures (LVF: mostly at the peak or the transition of peak to trough; PS: mostly during the transition of trough to peak). Consequently, the coupling phase of HFOs and low-frequency waves could represent the type and pattern of seizure onset [130].

5.3. HFOs & Spikes

Interictal spikes reflect synchronous postsynaptic potentials generated by hyperexcitable neurons in the epileptogenic networks [131], and spikes can further repetitively and transiently disrupt the functionality of physiological networks involved in cognitive processing [132, 133]. Therefore, spike-free ripples located outside the SOZ represent spontaneous physiologic rhythms in the human neocortex [134]. pHFOs often occur with spikes [21, 135] and this cooccurrence is a specific marker of the SOZ [21]. HFOs have been thought to reveal microscale epileptogenic network agitation, and spikes indicate the widespread propagation of abnormal discharges over the macroscale epileptogenic network [136, 137]. This concept may help explain the central role of SOZ in the epileptogenic network, since abnormal discharges from the SOZ could propagate to larger networks through spike spreading.

6. HFOS DEFINE DIFFERENT PATHOLOGIES IN EPILEPTOGENIC NETWORK

Neuroimaging and network neuroscience have brought forward tools to profile local lesions, whole-brain anomalies, and large-scale networks [138], but have neglected the differences in mac-microscale structural and functional organization. In other words, among the common area lesions, different pathological types may have different intrinsic epileptogenicities, and the importance in the epileptogenic network may also vary. Their different levels of epileptogenicity are also reflected by different HFO characteristics in the HFO network from the microscale. In 2015, Gotman's group investigated HFOs with different pathologic substrates and discovered that the rates of HFOs are higher in focal cortical dysplasia (FCD), mesial temporal sclerosis, and nodular heterotopia (NH) than in atrophy, polymicrogyria, and tuberous sclerosis [139]. However, as one zooms in on the anatomic areas of each lesion, the phenomena become more complex. For example, (1) the highest HFO area is not always located in NHs and some NHs may not be responsible for seizure onset [140-142]; (2) the HFO rates differ greatly in different locations and types of FCD, with the highest HFOs detected in the borders of the MRI-visible dysplastic lesion [139] and in FCD type II [143]. These studies show how different pathologies can affect local neuronal circuits. A distinct pattern identified by HFO analysis may provide us the data at a certain scale where non-invasive imaging may not identify lesions [31].

7. DIRECTIONS AND CHALLENGES OF THE APPLICATION OF HFOS TO THE DIAGNOSIS AND TREATMENT OF EPILEPSY

The close correlation between HFOs/HFO networks and the epileptogenic network highlights the importance of HFOs in clinical practice and provides some new directions in the diagnosis and treatment of epilepsy. However, there are some challenges that must be overcome before the application of HFOs. Here, we would like to discuss how HFOs provide new insights in epilepsy diagnosis and treatment from the following three aspects: 1) using HFOs to assess seizure potentiality in high-risk populations; 2) using HFOs to evaluate the curative effect after ASM treatment; and 3) using HFOs to guide minimally invasive surgical treatment.

As mentioned above, HFOs can reflect the formation and progression of the microscale epileptogenic network much earlier than abnormal EEG discharges and clinical seizures. Therefore, broadband EEG monitoring is recommended in high-risk patients who have undergone an initial brain insult such as SE, traumatic brain injury, encephalitis, or febrile convulsion-induced cerebral trauma [86, 144]. The emergence of pathological HFOs as well as their spread and accumulation across HFO networks, may signal the occurrence of epileptic seizures long before the appearance of symptomatic features. However, the effect of HFO assessment is hard to define due to the small proportion of patients at risk of developing epilepsy, the lengthy latency period, and the strict technical and environmental requirements [145].

Based on the canonical view that epilepsy is caused by an imbalance of "excitation-inhibition", currently there are over 30 ASMs with diverse molecular targets to block excitatory mechanisms or enhance inhibitory ones through, for instance, modulating voltage-gated ion channels or synaptic transmissions [146-149]. However, there are still many challenges (*e.g.*, pharmacoresistance, side effects, failure to prevent epileptogenesis or to treat comorbidities) in the pharmacological treatment of epilepsies as of now [150-153]. For long, researchers have focused on the pathological changes at the molecular level, overlooking the potential integration of these changes at larger neuronal circuits. Since epilepsy is increasingly perceived as an epileptogenic network disorder, it is highly recommended to shift the medicine treatment strategy from the "molecular" level to the "circuit" level [154]. The multiscale hierarchical epileptogenic network theory provides us with new insights on ASMs research, like gene therapy, the regulation of related pathways and the targeting of specific neural circuits [154-157]. Interestingly, as HFOs are one essential element of epileptogenesis, some researchers try to modulate HFO generation to control seizures. Pardo-Pena *et al*. found that citalopram, a blocker of serotonin uptake to elevate serotonin levels, can reduce the occurrence of spontaneous FRs, the mean number of oscillation cycles per FRs event, and the average frequency of FRs [158]. In addition, Ventura-Mejía *et al.* discovered that carbenoxolone and quinine, two gap junction blockers, can decrease the mean number of FRs and the mean number of oscillation cycles per FR event [159]. And these medications have antiepileptic effects. Despite their hypothesis, none of the above studies can fully support HFOs being the promising targets in anti-epilepsy since these treatments took effect through regulating related pathological circuits, which was further reflected on HFOs [159]. In this manner, HFOs seem to be one sensitive biomarker of epileptogenic network from microscale. In other words, HFOs seem to be one sensitive biomarker of the microscale epileptogenic network.

Generally, the efficacy of a ASM treatment is assessed based on the appearance of subsequent clinical episodes, which can be easily missed in the infant population and during sleep. Since the HFO characteristics correspond to the epileptogenic network states, HFO analysis provides a more reliable method to evaluate the efficacy of ASMs. For instance, an obvious reduction of HFOs represents the downregulation of the overall epileptogenic network excitability. Since the CFCs between HFOs and other signal bands participate in the diffusion of abnormal discharges in multiscale, a decreased CFC suggests better effects of the ASMs [160]. However, this monitoring is usually performed through the noninvasive HFO analysis based on scalp EEG [99, 161, 162], which is greatly attenuated by the skull or other blocking tissues and easily interfered by muscles and movements. In addition, the minimal HFO generation and the limited conduction make them difficult to be visualized in scalp EEG, especially for those originating from deep lesions [163]. As a result, recent studies on using HFOs to predict the efficiency of ASMs are mostly limited in pediatric patients with thinner skulls and specific epilepsy types [164]. For example, in 2021, Wang *et al.* demonstrated that changes in terms of number, spectral power, and channel number of scalp-ripples are closely related to the severity of epilepsy and can indicate disease susceptibility in patients with infantile spasms after adrenocorticotropic hormone (ACTH) treatment [98].

For epilepsy patients that react poorly to ASMs and eventually develop refractory epilepsy, EZ removal surgery is an optimal option to reach a seizure-free status [165]. However, the concept of the epileptogenic network provides us a new perspective that the disruption of critical nodes related to the epileptogenic network instead of complete removal is enough to stop seizures [30]. Due to the advancements in modern imaging techniques and stereoelectroencephalogram (SEEG), RF-TC has become a substitute for open surgery. In comparison with a conventional operation, RF-TC causes less damage and, therefore will show wider applicability in patients [166], especially those with multiple lesions or with EZs located near or inside the eloquent areas. This method enables selective destruction of critical epileptogenic nodes and real-time monitoring of dynamic changes in the epileptogenic network. In comparison to ECoG recordings during operation, RF-TC can also avoid the variations caused by anesthesia effects [167]. Therefore, with real-time dynamic SEEG monitoring, the HFO network and CFC features can be mapped to portray the epileptogenic network and identify essential hubs as damage targets before RF-TC and network abruption or remodeling can be monitored during RF-TC. After RF-TC, it is also highly recommended to maintain wide-band SEEG recordings for several days to compare the HFO characteristics and network changes to predict long-term outcomes and guide treatment steps. Nevertheless, it should be noted that, intracranial HFO network analysis based on SEEG can capture signals from only a very limited volume. Thus, the reliability of HFO analysis and the effectiveness of RF-TC largely depend on the complete coverage of all suspicious areas by the intracranial electrodes. Further discussion is needed on the definition of essential HFO network hubs and their correlation with similar counterparts in epileptogenic networks.

CONCLUSION

In conclusion, HFOs, as a biomarker of epilepsy, may also behave like networks and are closely related to the epileptogenic network. Assessment of HFOs/HFO network can provide the means to explore the epileptogenic network at the microscale neuronal-circuit level and better understand the interactions between different scales of the network. Assessments of the HFO and epileptogenic networks can also provide new insights to apply HFOs in the diagnosis and treatment of epilepsy. Conversely, there are also some challenges that need to be overcome. In the future, more precise evidence of the HFO and epileptogenic networks, in addition to data from a large number of practical studies based on big datasets, are required to further prove the validity of the network concept and HFO application.

LIST OF ABBREVIATIONS

AC	=	Alternating current
ASM	=	Anti-seizure medication
BOLD	=	Blood-oxygen-level-dependent
BPS	=	Bursts of population spikes
CFC	=	Cross-frequency coupling
EC	=	Effective connectivity
ECoG	=	Electrocorticography
EEG	=	Electroencephalography
ES	=	Epileptic spasms
EZ	=	Epileptogenic zone
FC	=	Functional connectivity
FCD	=	Focal cortical dysplasia
FR	=	Fast ripple
GABA	=	Gamma-Aminobutyric acid
HFO	=	High-frequency oscillations
HYP	=	Hypersynchronous onset
LVF	=	Low-voltage-fast onset
NH	=	Nodular heterotopia
NREM	=	Non-rapid eye movement
PLI	=	Phase lag index
REM	=	Rapid eye movement
RF-TC	=	Radiofrequency thermocoagulation
SC	=	Structural connectivity
SE	=	Status epilepticus
SEEG	=	Stereoelectroencephalogram
SOZ	=	Seizure onset zone
TLE	=	Temporal lobe epilepsy

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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