FULL-LENGTH ORIGINAL RESEARCH

Pathologic substrates of focal epilepsy influence the generation of high-frequency oscillations

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Summary

Objective: **Although a clear correlation has been observed between high-frequency oscillations (HFOs) and the seizure-onset zone in distinct lesions, the role of the underlying pathologic substrates in the generation of HFOs is not well established. We aimed to investigate HFO correlates of different pathologic substrates in patients with drug-resistant epilepsy, and to examine the relation of HFOs with the anatomic location of the dysplastic lesion and surrounding tissue in patients with focal cortical dysplasia (FCD).**

Methods: **We studied consecutive patients with drug-resistant epilepsy who underwent intracranial electroencephalography (iEEG) investigations with depth electrodes at the Montreal Neurological Institute and Hospital, between November 2004 and May 2013. Inclusion criteria were the following: a focal lesion documented by magnetic resonance imaging (MRI); EEG recording at a 2,000 Hz sampling rate; and seizures starting from depth electrode contacts placed in lesion and perilesional tissue.**

Results: **Thirty-seven patients (13 FCD, 12 mesial temporal sclerosis, five cortical atrophy, three polymicrogyria, three nodular heterotopia, and one tuberous sclerosis) were included; 18 were women (median age 34). Ripples and fast ripples were found in all lesion types, except tuberous sclerosis, which showed no fast ripples. There was a significant difference in rates of ripples and fast ripples across different lesions ($p < 0.001$), with higher rates in FCD, mesial temporal sclerosis, and nodular heterotopia than in atrophy, polymicrogyria, and tuberous sclerosis. Regarding patients with FCD, HFOs rates differed significantly across the three types of tissue (lesional, perilesional, and nonlesional; $p < 0.001$), being higher within the borders of the MRI-visible dysplastic lesion, followed by the surrounding area, and rare in the remote cortex.**

Significance: **Our findings suggest that in patients who are all intractable, the HFO rates vary with different pathologies, and reflect different types of neuronal derangements. Our results also emphasize the potential usefulness of HFOs as an additional method to better define the extent of the epileptogenic dysplastic tissue in FCD.**

KEY WORDS: **High-frequency oscillations, Epileptogenic lesions, Focal epilepsy, Intracranial stereo-EEG, Focal cortical dysplasia.**

Structural lesions of the cerebral cortex are often associated with medically intractable focal epilepsies.[1] Improvements in neuroimaging techniques have increased our ability to identify the extent and nature of cerebral lesions associated with epileptic seizures.[2,3] However, not all magnetic resonance imaging (MRI)–visible lesions in patients with epilepsy present unequivocal epileptogenicity. The most frequent pathologies identified in drug-resistant focal epilepsy are mesial temporal sclerosis (MTS), cortical atrophic/gliotic lesions, vascular malformations, tumors,

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and malformations of cortical development (MCDs). The relation of these lesions with the epileptogenic zone is complex and variable among different patients, and this variability likely depends on their type, extension, and location. In patients with temporal lobe epilepsy and unilateral MTS, for instance, the seizure-onset zone (SOZ) is typically limited to the lesional area and, in the majority of cases, resection of the mesial temporal structures leads to seizure freedom.[4,5] In other types of brain lesions, such as MCD or cortical atrophy with gliotic scars seen in the context of posttraumatic epilepsy, the epileptogenic zone often includes an area larger than the MRI-visible lesion, and more often seizures persist after surgery.[6–8] Moreover, different pathologic substrates seem to have different grades of epileptogenicity and differ in their ability to generate seizures.

In the past two decades, high-frequency oscillations (HFOs), namely ripples (80–250 Hz) and fast ripples (FRs, 250–500 Hz), have received considerable attention in epilepsy research. HFOs are emerging as reliable biomarkers of epileptogenicity and good indicators of seizure-onset areas.[9–11] Compared to spikes, interictal HFOs are more specific to the SOZ.[10,12] In addition, HFOs seem to be good markers of disease activity and appear to play an important role in ictogenesis.[13,14] Although a clear correlation has been observed between HFOs and the SOZ with different pathologies, it remains unclear whether different pathologic substrates influence the generation of interictal HFOs. Initially, HFOs were recorded in patients and animal models with temporal lobe epilepsy with hippocampal sclerosis.[15] Later, HFOs were also described in epilepsy patients with other types of lesion, such as focal cortical dysplasia (FCD), tumors, nodular heterotopia (NH), and cortical tubers.[11,16–18] Investigations on HFOs in different lesion types remain sparse, and findings diverge. In a study of focal epilepsy with various causes, Urrestarazu et al.[16] found that pathologies such as FCD seem to generate HFOs more than others. In contrast, Jacobs et al.[10] later found no relationship between HFO rates and distinct types of lesion, including MTS, FCD, and NH.

In the case of FCDs, the delimitation of the border of the dysplastic tissue by imaging is often difficult.[19] Specific interictal and ictal EEG patterns may help the identification of the dysplastic cortex.[20,21] Still, these markers of epileptogenicity are not sufficient because seizure freedom is not always achieved.[7] Because HFOs often co-occur with spikes and are linked to regions of seizure onset, they might be a useful tool to better delineate dysplastic tissue.[16]

The first aim of this study was to determine if different pathologic lesions influence the generation of interictal HFOs in patients with drug-resistant focal epilepsy. In addition, in epileptic patients with FCDs, we examined the relation of HFOs with the anatomic location of the dysplastic and surrounding tissues.

Materials and Methods

Patients

We studied consecutive patients with drug-resistant focal epilepsy who underwent intracranial electroencephalography (iEEG) investigations with depth electrodes at the Montreal Neurological Institute and Hospital, between November 2004 and May 2013. Inclusion criteria for the study were the following: (1) a focal lesion documented by MRI; (2) EEG recording at a 2,000 Hz sampling rate; and (3) seizures starting from depth electrode contacts placed in lesion and perilesional tissue. Patients who had clinical manifestations preceding the electrographic onset in all seizures were excluded.

Stereo-EEG (SEEG) recording methods

Depth electrodes (DIXI or electrodes manufactured on site) were implanted stereotactically using an image-guided system (SNN Neuronavigation System or Medtronic StealthStation S7, Louisville, CO, U.S.A. and Medtech ROSA Robotic System, Montpellier, France) as described previously.[22] The electrodes manufactured on site consist of a stainless steel central core coated with Teflon, with nine contacts, 0.5–1 mm in length and 5 mm intercontact distance. DIXI Medical electrodes are composed of 5–18 contacts, 2 mm in length and 1.5 mm apart. Electrode placement was tailored according to clinical history, seizure semiology, results of noninvasive investigations (surface EEG and imaging), and cognitive function testing. SEEG studies were recorded using the Harmonie long-term monitoring system (Stellate, Montreal, QC, Canada), with a low-pass filter at 500 Hz and sampled at 2,000 Hz. Referential montage with an epidural reference placed contralaterally to the suspected epileptogenic zone was used during the acquisition.

Channel selection and classification

The electrode and contact localizations were defined according to a postimplantation or explantation MRI, and, if not available, the Neuronavigation System–generated images or coregistration of the postimplantation computerized tomography (CT) with the preimplantation MRI was used.

Electrode contacts were classified as *lesional* if located within the visible borders of the lesion on the MRI. In addition, in patients with FCD, contacts located up to 1 cm from the border of the lesion were classified as *perilesional,* and *nonlesional* if located more than 1 cm from the lesional border.

EEG recordings were analyzed using a bipolar montage. Channels containing at least one lesional contact were classified as lesional channels. Channels with one perilesional and one nonlesional contact were classified as perilesional channels.

Channels showing the first unequivocal ictal iEEG change from the background leading to a clear seizure discharge at the time of seizure onset were classified as SOZ channels, and were defined as part of the clinical investigation by a board-certified neurophysiologist (FD), independently of the present study. Channels not involved at the time of seizure onset were classified as non-SOZ channels.

HFO marking

We selected interictal samples of 5–10 min of slow-wave sleep excluding at least 2 h before and after a seizure. HFOs were marked visually in the first minute of each selected interictal EEG sample, using a bipolar montage made of adjacent contacts, by two separate reviewers (PP and TFM). The concordance between marked HFOs was assessed using Cohen's kappa coefficient (κ), computed for each bipolar channel. If $k < 0.6$, both reviewers reanalyzed the corresponding channel and established a consensus. The remaining 4 min were then marked by one of the reviewers based on the consensus reached.

The identification and marking of HFOs were performed according to the method developed at the Montreal Neurological Institute, as described previously.[10]

Statistical analysis

After marking all events, rates of ripples and FRs per minute for each channel (computed for every 1-min interval in the data) were calculated using a MATLAB (The MathWorks Inc., Natick, MA, U.S.A.) program.

Lesional channels were first classified in six groups, according to the type of underlying lesion: MTS, FCD, NH, polymicrogyria (PMG), tuberous sclerosis complex (TSC), and cortical atrophy (CA). Lesional channels were then divided according to their relation to the seizure onset in lesional/SOZ and lesional/non-SOZ channels. Rates of HFOs were then compared across these groups.

In patients with FCD (n = 13), all channels were categorized into three groups, according to their location with respect to the lesion: lesional, perilesional, and nonlesional. Rates of HFOs were then compared across the three groups.

The Kruskal-Wallis test was used for all comparisons. The Bonferroni correction was applied to adjust for multiple testing. The level of significance was set at 0.05. All analyses were performed using SPSS 19.0 (IBM, Chicago, IL, U.S.A.).

Results

Thirty-seven patients were included in the study (18 women). The median age was 34 years (range 16–56 years), and the median age at seizure onset was 9 years (range 1–49 years). Thirteen patients had FCD, 12 had MTS, 5 had local/regional CA, 3 had PMG, 3 had NH, and one had TSC. Among the 13 patients with FCD, one did not undergo surgery, 4 had no histopathologic report, one had FCD without further classification, 2 had FCD type IIa, and 5 had FCD type IIb.

HFOs and different lesions

The first aim of this study was to investigate whether interictal HFO rates correlate with different types of lesion. Only channels inside the lesion were included in this analysis. A total of 420 lesional channels were analyzed, and distributed as follows: 110 in FCD; 67 in MTS; 99 in local/regional CA; 81 in PMG; 56 in NH, and 7 in TSC.

Ripples and FRs were found in all lesion types, except TSC, which showed no FRs (Fig. 1). There was a statistically significant difference in rates of ripples and FRs across different lesions ($p < 0.001$) (Fig. 2), with higher rates in FCD, MTS, and NH, and lower rates in PMG, CA, and TSC.

In previous studies, HFOs have been related to seizure-onset areas. Hence our results could be largely influenced by the fact that the SOZ is in the lesion and may not, as a result, reflect lesional tissue. We therefore compared HFO rates in lesional contacts *inside* the SOZ and lesional contacts *outside* the SOZ. Ripple and FR rates differ signifi-

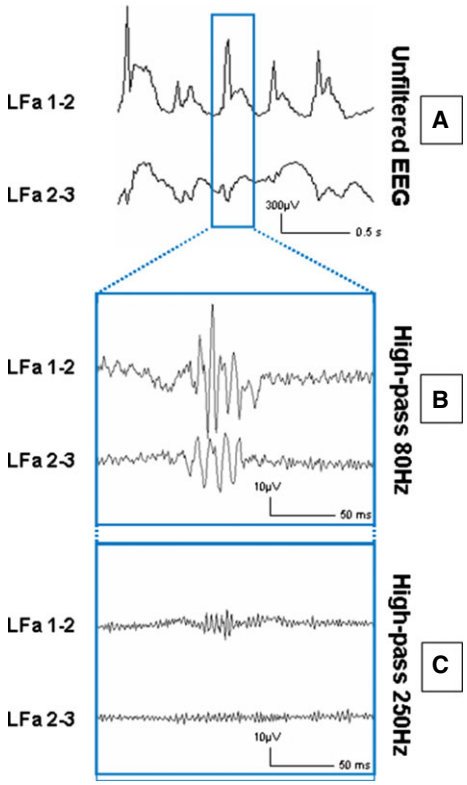

Figure 1.
Intracranial EEG recording of a patient with focal cortical dysplasia in the frontal lobe. The unfiltered EEG (**A**) showing frequent spikes in the deepest contacts (LFa 1–2 and 2–3) of the depth electrode inserted in the dysplastic lesion. The blue section in **A** is expanded in time and amplitude, demonstrating the co-occurrence of ripples (**B**) and fast ripples (**C**). LFa, left frontal anterior.

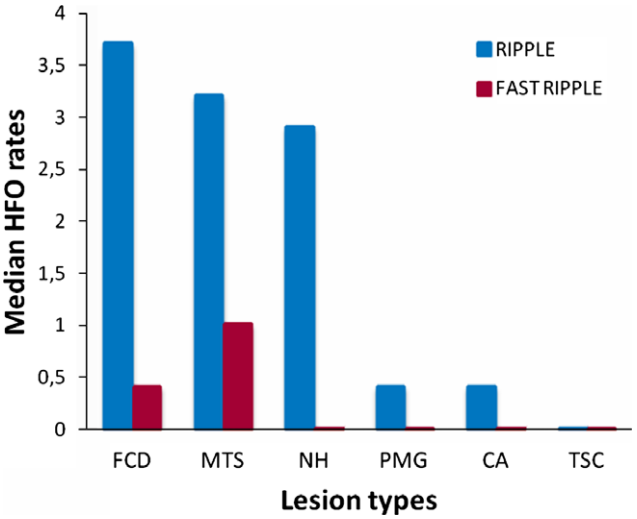

Figure 2.
Histogram illustrating differences in ripple and FR rates across different lesions. Median ripple and FR rates were significantly higher in focal cortical dysplasia, mesial temporal sclerosis, and nodular heterotopia as compared to the other lesions ($p < 0.001$). Some median rates are zero because most channels in the corresponding category had no HFOs, but some channels did.
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cantly across different lesions in both SOZ and non-SOZ areas (Table 1), confirming that our earlier results were primarily reflecting a lesion effect rather than an effect of the SOZ. Of interest, similar ranking of HFO rates across lesions was seen in SOZ and non-SOZ channels, higher in MTS, FCD, and NH than in CA, PMG, and TSC.

Relationship of HFOs with FCD and surrounding tissue

To assess the relation of HFOs with the MRI-visible FCD and the surrounding brain tissue, we analyzed all channels (636) for the 13 patients with FCD. Rates of ripples and FRs were compared in lesional, perilesional, and nonlesional channels.

Ripple rates differed significantly across the three types of channels ($p < 0.001$). Rates were significantly higher in lesional compared to perilesional channels ($p < 0.001$), whereas no statistically significant differences were found between perilesional and nonlesional channels ($p = 0.08$) (Table 2).

FR rates also differed significantly across the three tissue channels ($p < 0.001$). They were significantly higher in lesional than in perilesional channels ($p < 0.01$). As opposed to ripples, however, FR rates were significantly higher in perilesional as compared to nonlesional channels ($p < 0.05$) (Table 2).

To assess if our findings reflect again the SOZ rather than the three types of tissues, a separate analysis was performed comparing rates of both events (ripples and FRs) across the three tissue types only in channels inside the SOZ. Significant difference of HFO rates across lesional, perilesional, and nonlesional channels inside the SOZ was limited to ripples ($p = 0.047$). Of interest, perilesional channels were associated with higher rates of ripples compared to lesional channels (Fig. 3). FR showed similar results, with higher rates in perilesional channels than in lesional channels, but this did not reach statistical significance ($p = 0.057$) (Fig. 3).

When limiting the analysis to channels outside the SOZ, ripple rates ($p < 0.001$), but not FR rates ($p = 0.1$), differed significantly across the three types of tissue in patients with FCD (Fig. 3).

Discussion

In this study, which assessed HFO correlates of six different epileptogenic lesions in a sizable cohort of patients undergoing iEEG investigations, we found that lesions differ in their propensity to generate HFOs. Specifically, MTS, FCD, and NH displayed higher HFO rates compared to PMG, TSC, and CA. These findings are in apparent contrast to those of a previous smaller study,[11] which did not find differences in HFOs across lesions. However, only three lesions were analyzed, that is, MTS, FCD, and NH, which also displayed similar HFO rates in the present investigation. Therefore, our findings in a larger number of patients and types of lesions expand the level of understanding of underpinnings of HFOs.

Different lesion types have specific neuronal derangements with particular pathophysiologic mechanisms and

Table 1. HFOs per minute in lesional contacts inside and outside the SOZ for the six lesion types

	Median (range) rates of HFOs in lesional SOZ channels						
	FCD	MTS	NH	PMG	CA	TSC	p-Value
Ripples	4.3 (0–170.2)	5 (0–107.6)	7.2 (0–198.4)	0.8 (0–52.8)	2.2 (0–68.8)	n/a	<0.001
FRs	1.6 (0–194.6)	1.8 (0–70.8)	0 (0–205)	0 (0–29)	0 (0–12.6)	n/a	<0.001
	Median (range) rates of HFOs in lesional non-SOZ channels						
	FCD	MTS	NH	PMG	CA	TSC	p-Value
Ripples	1.5 (0–40.8)	2.5 (0–105.7)	1 (0–136.6)	0.2 (0–62.8)	0.4 (0–220.4)	0 (0–2.3)	<0.05
FRs	0 (0–16)	0.4 (0–43)	0 (0–2.4)	0 (0–6.6)	0 (0–39.2)	0 (0–0)	<0.01

Table 2. HFOs per minute in lesional versus perilesional versus nonlesional channels in patients with FCD

	Types of tissue in patients with FCD		
	Lesional (n = 110)	Perilesional (n = 41)	Nonlesional (n = 485)
Ripples			
Median (range)	3.7 (0–170.2)	0.4 (0–43.6)	0 (0–148.4)
p-Value	<0.001	0.08	
FRs			
Median (range)	0.4 (0–194.6)	0 (0–23)	0 (0–72.8)
p-Value	0.01	<0.05	

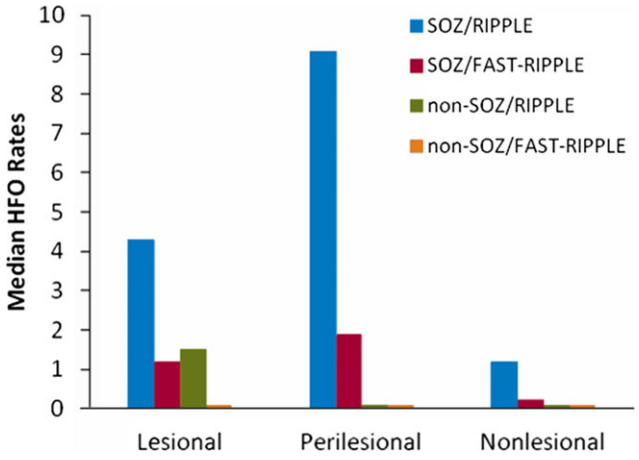

Figure 3.
Median rates of ripples and FRs in different types of tissue in patients with FCD, separately for channels inside the SOZ and those outside. Ripple rates were higher in the perilesional than in lesional tissue in SOZ channels ($p = 0.047$). FRs also showed higher rates in perilesional tissue than inside the lesion, but this did not reach statistical significance ($p = 0.057$). SOZ: seizure-onset zone.

various degrees of epileptogenicity. It has been suggested that HFO rates depend on the epileptic disease activity of the underlying tissue.[10,14,23] All lesions analyzed in this study were highly epileptogenic, since we included only patients with severe refractory epilepsy who underwent invasive neurophysiologic investigation and had seizures starting in lesional tissue. Despite their high degree of epileptogenicity, these different lesions also differed significantly in their ability to generate HFOs. It is therefore possible that HFO rates are more likely to reflect distinct underlying neuronal derangement rather than different disease activity.

All cellular and network circuitries involved in the generation of fast activity remain to be elucidated. Synaptic reorganization, neuronal loss, and abnormal neurons or glial cells may interact in the generation of ripples and FRs. In line with earlier observations,[10,11] we found that MTS is associated with high rates of HFOs. MTS is characterized by various degrees of neuronal loss in the mesial temporal structures, mainly in the hippocampus,[24] usually accompanied by granule cell dispersion in the dentate gyrus, mossy fiber sprouting, and synaptic reorganization leading to disruption of hippocampal circuitry.[25,26] In a study in epileptic rats, a strong correlation was found between the power of FRs and the degree of neuronal loss, but not with the degree of mossy fiber sprouting,[27] suggesting that neuronal death may be related with the generation of HFOs. However, cortical atrophy, a type of lesion also related with neuronal loss, showed very low rates of HFOs in our study. Hence, other changes, in addition to cell loss, are necessary for the generation of high-frequency activity.

Cortical tubers and FCD are MCDs related to abnormal glial and neuronal proliferation, and they share similar histologic abnormalities including balloon cells and giant dysmorphic neurons.[28] However, in our study, FCD, including type IIb, showed high rates of HFOs, while TSC revealed very few. Although this marked contrast in HFO rates between two morphologically similar lesions might suggest distinct neurophysiologic characteristics, this conclusion is limited by the fact that only one patient had TSC. Different histologic subtypes of FCD (with and without balloon cells) have been identified and their ability to generate HFOs differs.[14,29] We did not subclassify the dysplastic lesions in our patients; therefore, the heterogeneity of the FCD group could be another explanation for the difference in HFO rates across the two types of lesions (FCD and TSC).

In patients with FCDs, we compared the ability of the lesion to generate HFOs, with the perilesional tissue and with cortical tissue remote from the lesion border. We demonstrated that HFO rates differ significantly across these different types of tissue (lesional, perilesional, and nonlesional), being higher within the borders of the MRI visible dysplastic lesion, followed by the surrounding area and rare in remote cortex. Similarly, another study analyzed the distinction of lesional and nonlesional tissue in 15 patients with drug-resistant focal epilepsy caused by FCD, using more traditional methods—interictal spikes—and found that lesional tissue shows significantly higher numbers of slow repetitive spikes in comparison with normal tissue.[34] FCDs

are characterized by a lack of normal cortical lamination, often associated with dysmorphic giant cells and undifferentiated balloon cells.[30] In contrast with other structural epileptogenic neocortical lesions (e.g., cysts, vascular lesions, and tumors) in which the surrounding tissue is believed to be responsible for generating the seizures, FCD has been demonstrated to be highly and intrinsically epileptogenic, and the extent of removal of the lesion identified either by MRI or by cortical visual inspection predicts surgical outcome in patients with refractory epilepsy.[6–8,31,32] Jacobs et al.[11] investigated four patients with FCD and did not find significant differences in ripple and FR rates in lesional versus nonlesional tissue, but revealed a significantly higher FR rate within the SOZ when compared to regions outside this zone. Urrestarazu et al.[16] performed HFO analysis of one patient with FCD and found FR to be more frequent within the lesion and outside the SOZ, and suggested that FR could be a marker of this lesion type. There is evidence that γ-aminobutyric acid (GABA)ergic interneurons are decreased in dysplastic cortical regions, compared with adjacent nondysplastic cortex.[31] Moreover, it has been demonstrated that HFO activity and spatial extent is controlled by blocking of local inhibition.[33] Therefore, the structural and functional disorganization of dysplastic tissue may explain the higher rates of ripples and FRs inside the lesion when compared to other brain regions.

Analysis of HFO rates in dysplastic lesion and tissue beyond but remaining inside the seizure-onset zone, revealed higher rates of HFOs in the perilesional tissue when compared to the lesion itself. Poor surgical outcome in operated patients with FCD was suggested to reflect the difficulty in identifying the margins of the lesion on imaging and at surgery.[20] Histologic analyses in patients with FCD have shown that microscopic dysplastic abnormalities can occur in the context of a normal MRI.[19,20] In addition, in previous studies using intraoperative electrocorticography in patients with FCD, continuous epileptogenic discharges were recorded not only in the visible dysplastic cortex but also in the adjacent neocortex,[6,20] suggesting epileptogenicity beyond the visible lesion. Our results suggest that measures of HFOs may provide an index of the real lesion extension, and help guide surgery. Histologic analysis of the removed tissue would be necessary to confirm this hypothesis; our histopathological data do not allow a reliable analysis of lesional versus perilesional tissue. Moreover, a comparison of seizure outcome among patients who had different extents of resection, according to the presence of HFOs, would help confirm the value of HFOs in defining this extent. This may be the aim of further studies.

One may wonder if the SOZ or the pathology is the primary determinant of the rate of HFOs. Several studies have demonstrated that, for a given patient, the channels with the highest HFO rate have a high probability of being in the SOZ. We demonstrate here that the absolute rate of HFO is influenced largely by the lesion type, but that within a lesion type, the rate of HFO remains highest in the SOZ. The HFO rate inside the SOZ and outside the SOZ, both being within the lesion, fluctuate in parallel (higher in some lesions than in others).

Our study has limitations. Lesion types were classified according to the neuroimaging characteristics. Although high-definition neuroimaging and image processing can assist clinicians in the identification and differentiation of structural lesions, neuroimaging cannot assess histopathologic subclassification of some lesions, such as FCD. Further studies with detailed histologic examination, and ideally with immunohistochemistry evaluations, will improve our knowledge of how different pathologic substrates influence the generation of HFOs. In addition, the definition of the SOZ is always limited by the limited spatial sampling of intracerebral electrodes, whether they are depth or subdural electrodes.

In summary, our study places a context around the established association between HFOs and the SOZ by establishing the influence of underlying pathology. From a clinical perspective, our results stress the necessity of differentiating lesions in the analysis of HFOs. Moreover, varying rates of HFOs across different regions of cortex within and surrounding the dysplastic lesion in FCD may support the hypothesis that cortical disorganization may vary largely across these regions. These results also emphasize the potential usefulness of HFOs as an additional method to guide and better define the extent of the epileptogenic dysplastic tissue in patients with FCD and drug-resistant epilepsy.

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Disclosure

The authors have no conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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