Epilepsy & Behavior Reports 31 (2025) 100776

Contents lists available at ScienceDirect

Epilepsy & Behavior Reports

journal homepage: www.elsevier.com/locate/ebcr

Investigation of the relationship between 0.5–1200 Hz signal characteristics of cortical high-frequency oscillations and epileptogenicity through multivariate analysis

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ARTICLE INFO

Keywords:
Epilepsy surgery
Multivariate logistic regression analysis
Phase-amplitude coupling
Ripple
Very high-frequency oscillations

ABSTRACT

Fast ripples (FRs) (250–500 Hz) on the electroencephalogram (EEG) are closely related to epileptogenicity and are important to determine cortical regions resected in epilepsy surgery. However, FR-related epileptogenicity may be variable, and may depend on information associated with FRs. We enrolled nine epilepsy patients who had undergone intracranial 5 kHz-sampling-rate EEG for surgical treatment and had final Engel class I outcomes. Three electrodes were selected from each epileptogenic area (EA) and the unlikely EA (the region outside the EA) in each patient. Up to 100 candidate FRs were automatically detected from interictal nocturnal EEG at each of the selected electrodes and were visually reviewed independently by two researchers. Multivariate logistic regression analysis was performed using the frequency and log-power value of the corresponding FRs, presence of concurrent spike, ripple, very-high-frequency oscillations (vHFO)1 (500–600 Hz), and vHFO2 (600–1200 Hz), and whether the timing of the spectral peak of corresponding FRs was in the peak–trough or trough–peak transition of each slow activity (0.5–1, 1–2, 2–3, 3–4, and 4–8 Hz) as independent variables. Factors significantly related to epileptogenicity were FR power, the concurrent presence of spike and vHFO2, coupling with 0.5–1 and 1–2 Hz slow waves in the peak–trough transition, and coupling with 3–4 and 4–8 Hz slow waves in the trough–peak transition. Multifactorial analysis of FRs may increase their usefulness, potentially leading to improved treatment outcomes in epilepsy surgery.

1. Introduction

High-frequency oscillations (HFOs) are classified into ripples (80–200/250 Hz) and fast ripples (FRs) (250–500 Hz). HFOs, especially FRs, are indicated to be a potential biomarker for epileptogenicity and, in epilepsy surgery, resection of the brain regions with FRs in addition to the seizure onset zone (SOZ) may achieve a better seizure outcome [1–4]. However, there are also physiological HFOs, and it is often difficult to distinguish them from pathologic HFOs [5–7]. In individual cases, complete resection of the brain area with HFOs does not necessarily lead to a better outcome and, conversely, seizure control may be achieved without resecting the brain area with HFOs [8,9].

HFOs with frequencies above 500 Hz are termed very-high-frequency oscillations (vHFOs). Ictal and interictal vHFOs are suggested to be more specific biomarkers for the epileptogenic zone compared with traditional HFOs [10,11].

Phase-amplitude coupling (PAC) is a cross-frequency coupling analysis that evaluates coupling between the amplitude of high-frequency activity and the phase of the low-frequency band [12,13]. A stronger coupling indicates a stronger relationship between the two frequency bands. PAC is suggested to be more valuable than HFOs alone in localizing the epileptic zone [14–18]. Pathological HFOs may be

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https://doi.org/10.1016/j.ebr.2025.100776
Received 1 March 2025; Received in revised form 23 April 2025; Accepted 23 April 2025
Available online 24 April 2025

preferentially coupled with slow oscillations at 3–4 Hz more than with slow oscillations at 0.5–1 Hz, which are more often coupled with physiological HFOs. Amiri et al. demonstrated that not only the frequency of the coupled slow oscillations but also the phase of coupling of HFOs and slow oscillations may help to identify the SOZ [17].

Each marker of epileptogenicity may be more valuable when evaluated in conjunction with other associated information than when evaluated alone. For example, interictal epileptiform discharges (IEDs), the most widely used marker of epileptogenicity, are thought to have variable degrees of pathological significance, and it has also been reported that IEDs accompanied by HFOs are highly pathologic [19]. We hypothesized that the degree of FR-related epileptogenicity may be

Table 1
Demographic data of the patients.

Case	Age at operation (yrs)	Sex	Seizure type	Operation	Etiology/ pathology	Analyzed electrodes EA electrode	No. of FRs*	FR rate (/min)†	Unlikely EA electrode	No. of FRs*	FR rate (/min)†	EEG data length (min)	Follow-up period (mos)	Engel class
1	23	F	FIAS, FBTCS	L ATL, additional L TL	Acute encephalopathy during infancy, HS ILAE Type 1	cortical	0/79	0.000	cortical	0/100	0.000	315	29	IA
							0/75	0.000		0/65	0.000			
							0/100	0.000		0/79	0.000			
2	17	F	FIAS, FBTCS	R ATL	FCD IIa	cortical	0/100	0.000	cortical	0/51	0.000	340	34	IA
							2/98	0.010		0/100	0.000			
						depth	92/8	8.783		0/77	0.000			
3	13	M	FIAS	R extended ATL	FCD IIa	cortical	71/29	1.728	cortical	64/36	0.923	132	53	IA
							64/36	1.441		70/30	1.481			
						depth	73/27	2.363		73/27	1.083			
4	23	M	FMS	R F lesionectomy	FCD IIb	depth	70/30	2.943	cortical	0/100	0.000	103	61	IA
							66/34	2.193		0/46	0.000			
							0/42	0.000		0/100	0.000			
5	19/21	M	FIAS/ FBTCS	R lateral TL/ additional R TL	HS ILAE Type 3	cortical	2/98	0.057	cortical	4/96	0.029	360	68/41	IA§
							9/91	0.716		20/80	0.195			
							0/100	0.000		1/92	0.003			
6	22	F	FIAS, FBTCS	R ATL	Unknown/no remarkable pathological findings	cortical	85/15	3.615	cortical	0/80‡	0.000	360	74	IB
							70/30	0.649		0/75‡	0.000			
							0/96	0.000		0/100‡	0.000			
7	14	M	FMS, FBTCS	R F (SMA + cingulate) lesionectomy	Unknown/no remarkable pathological findings	cortical	16/84	1.368	cortical	2/98	0.013	221	78	IA
							2/98	0.011		2/98	0.011			
							1/99	0.005		0/100	0.000			
8	16	M	FIAS	L F lesionectomy	FCD IIa	cortical	1/99	0.004	cortical	1/99	0.005	270	72	IA
							28/72	0.249		1/99	0.005			
							55/45	0.875		1/99	0.005			
9	34	F	FIAS, FBTCS	L T lesionectomy	ganglioglioma	cortical	5/95	0.167	cortical	1/99‡	0.032	90	29	IA
						depth	2/98	0.040		1/99	0.033			
							4/96	0.078		0/100	0.000			

M, male; F, female.
ATL, anterior TL; EA, epileptogenic area; F, frontal; FBTCS, focal to bilateral tonic-clonic seizure; FCD, focal cortical dysplasia; FIAS, focal impaired awareness seizure; FMS, focal motor seizure; FR, fast ripple; HS, hippocampal sclerosis; ILAE, International League Against Epilepsy; L, left; R, right; SMA, supplementary motor area; T, temporal; TL, temporal lobectomy.
*No. of identified FRs/discarded candidate FRs.
†Mean rate of FRs: 1.01/min in EA and 0.14/min in unlikely EA.
‡Electrodes in brain regions that were unlikely to be epileptogenic but resected in the surgical procedure.
§Although the final outcome was complete seizure suppression, the first operation resulted in seizure persistence with milder ictal symptoms.

dependent on the associated information. Therefore, we intended to investigate which components of spikes, ripples, vHFOs, and the frequency and phase of coupled slow waves are associated with FRs and are indicative of epileptogenicity through multivariate analysis. Unlike other studies that explored areas of strong epileptogenicity by FR power or occurrence rate, we aimed to find the differences in FR signal characteristics between areas of strong and weak epileptogenicity in this study.

2. Subjects and methods

2.1. Subjects

The subjects of the present study were nine epilepsy patients who had undergone intracranial 5 kHz-sampling-rate electroencephalogram (EEG) recording described below for surgical treatment at the Okayama University Hospital during the period between January 2017 and December 2021 and had final Engel class I outcome (age at operation ranging from 13 to 34 years; five men and four women; post-operative follow-up period ranging from 29 to 78 months) (Table 1).

2.2. Methods

The EEG was recorded using a Nihon-Kohden (Tokyo, Japan) Neurofax, mostly with a sampling frequency of 1,000 Hz, to have a sufficient number of seizures captured. During the period between the completion of the ordinary monitoring and the scheduled surgery, the EEG was digitized with a sampling rate of 5 kHz and a band-pass filter ranging from 0.8 Hz to 1,200 Hz in the expectation of capturing additional seizures with possibly more detailed information. Because recording with this high sampling rate is demanding for the system, Neurofax allowed usage of only the first 37 electrodes of the system. We used referential montages taking reference to the skull.

Interictal EEG data sampled at 5 kHz were selected from three electrodes in each of the epileptogenic areas (EA) and unlikely EA: the EA was defined based on the SOZ, video-recorded ictal semiology, neuroimaging findings, etc. through consensus of all research members in Okayama University. Unlikely EAs were regions outside of the EA, and the corresponding electrodes were selected to show the least epileptic activity: these electrodes were mostly outside the resected area, but some were from areas that were determined to be unlikely epileptogenic but had to be resected due to surgical techniques. An EEG was recorded using either cortical electrodes alone or a combination of cortical and depth electrodes. When selecting electrodes for EA and unlikely EA, the choice was made regardless of whether they were cortical or depth electrodes. The type of selected electrodes in each case is indicated in Table 1. The EEG data used were recorded with minimal artifacts during the night (11:00p.m. to 5:00 a.m.) when the patients were probably sleeping and were at least 60 min apart from any seizure.

First, in the data from each selected electrode, we automatically detected the first 100 (or < 100 depending on availability) candidate FRs using a program written by von Ellenrieder et al. for MATLAB (MathWorks Inc. Natick, MA, USA) [20], as in our previous studies [21–23]. This program was designed to detect HFOs as localized increments of signal power with a duration of at least four cycles in the narrow frequency bands based on a finite impulse response (FIR) filter. The candidate FRs were at least 1,000 ms apart.

Second, the automatically detected candidate FRs were shown as follows in temporally expanded and filtered EEG traces in panels (e.g., see Fig. 1). A program written in-house was used, and it employed a type of FIR filter based on the application of the discrete Fourier transform, zeroing parameter values outside of the specified frequency band, and the subsequent inverse Fourier transform causing no phase shift. We did not set any amplitude limit of slow activity for phase estimation. Fig. 1 **left top**: filtered slow activities with a temporal window of 1,000 ms and the band-pass frequency (BPF) of slow activity (0.5–1 Hz, 1–2 Hz, 2–3 Hz, 3–4 Hz, and 4–8 Hz, each) along with the original EEG trace (low-cut frequency [LCF] filter at 0.5 Hz). Fig. 1 **left bottom**: corresponding time–frequency power spectral analysis for FRs and other HFOs using the Gabor transform, which was the Fourier transform performed on

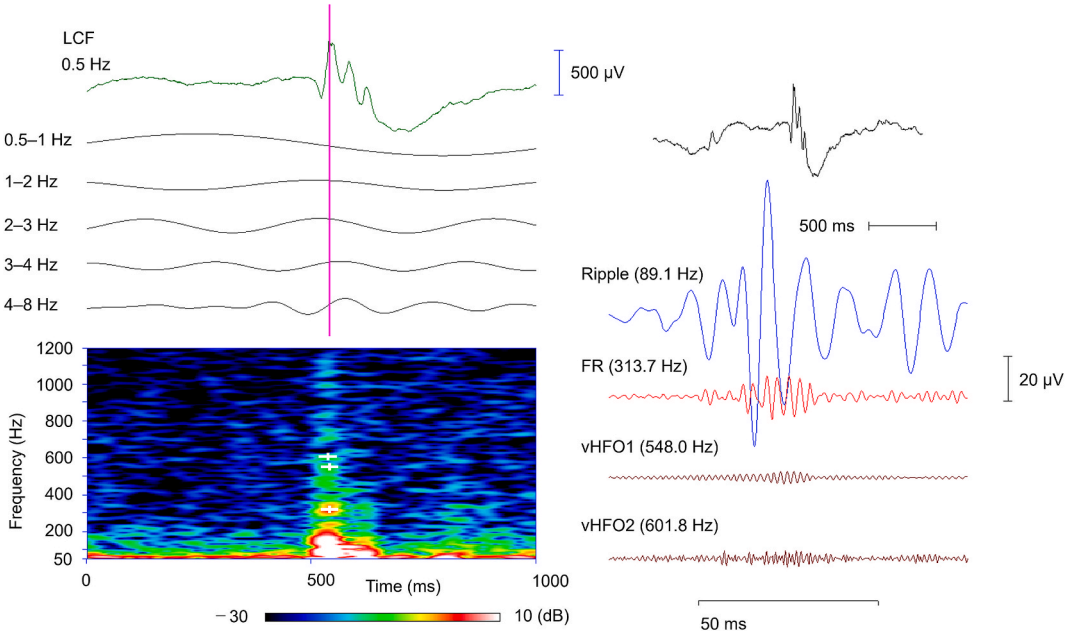

Fig. 1. Representative high-frequency oscillation panel. Analysis of intracranial EEG data recorded from Case 4 (Table 1). **Left side:** The top green waveform shows the raw EEG trace. The black waveforms below are extracted slow waves in the frequency bands of 0.5–1, 1–2, 2–3, 3–4, and 4–8 Hz, and the pink vertical line represents the FR coupled phase. The bottom plot shows the time–frequency spectrum, and the white crosses above the blobs indicate the detected HFOs in each frequency band. **Right side:** The top black waveform shows the raw EEG trace in ordinary time scale. The blue, red, and brown waveforms below are ripple, FR, vHFO1, and vHFO2, respectively, and the presence of these HFOs was defined as at least four consecutive oscillations. FR, fast ripple; LCF, low-cut filter; vHFO, very high-frequency oscillation.

1,024 data points (204.8 ms; frequency resolution 4.88 Hz) at each 2-ms time step with a sliding Gaussian window of 50-ms full-width half-maximum, with the frequency range of 50–1,200 Hz (the power peak, if any, in each high-frequency band being indicated with a white cross mark in the power spectrum). Fig. 1 **right top**: the original EEG trace with a temporal window of 2 s. Fig. 1 **right bottom**: high-frequency activities including candidate HFOs filtered with the BPF of 80–250 Hz (ripple), 250–500 Hz (FR), 500–600 Hz (vHFO1), and 600–1200 Hz (vHFO2) with a temporal window of 100 ms. The vHFO1 and vHFO2 bands were separated because the higher margin of the FR band is occasionally set at 600 Hz.

Two research members independently visually reviewed each panel with no clinical information to indicate the presence or absence of a concurrent spike in the original trace and each type of oscillation: activity was defined as present only when both reviewers agreed. HFOs should be composed of at least four consecutive waves. The rate of identified true FRs was computed in the corresponding EEG data for candidate FR detection in each selected electrode.

2.3. Statistical analysis

Univariate logistic regression analysis was used to determine whether each factor was related to epileptogenicity. Multivariate logistic regression analysis via the forward–backward stepwise selection method was used to investigate which of these factors were particularly related to epileptogenicity. We set whether the electrode was in the EA (Group E) or the unlikely EA (Group U) as the dependent variable. The independent variables included the frequency and log-power value of the corresponding FR, the presence or absence of concurrent spike, ripple, vHFO1, and vHFO2, and whether the timing of the spectral peak of the corresponding FR was in the peak-to-trough transition (descending phase) or trough-to-peak transition (ascending phase) of each slow activity. Candidate FRs that were judged as noise/artifacts void of actual FRs by either reviewer were excluded from the statistical analysis. A p-value < 0.05 was considered statistically significant for all analyses. The odds ratio (OR) was estimated to be statistically significant when a 95 % confidence interval (CI) did not encompass 1. For multivariate logistic regression analysis, when a p-value was < 0.05 in the model chi-squared test, and the 95 % CI of the OR did not encompass 1, it was considered significant regardless of the Wald test results. Statistical analyses were performed using R-4.1.2 (CRAN).

3. Results

3.1. Detection of fast ripples

There were a total of 5,081 candidate FRs, and both reviewers agreed to the presence of 959 FRs (718 in the resected EAs, 240 in the unlikely EAs remaining unresected, and one in the unlikely EA resected in the surgical procedure), there were 103 and 222 candidate FRs each of which was recognized by only one of the two reviewers. The mean rate of FRs was 1.01/min (range 0–8.78/min) in the EA and 0.14/min (range 0–1.48/min) in the unlikely EA (Table 1).

3.2. Predictive factors for epileptogenicity

The results of the univariate logistic regression analysis for each factor are shown in Table 2. The parameters of FR power, the concurrent presence of spike, ripple, and vHFO2, and coupling of FR with the trough–peak transition of 3–4 Hz and 4–8 Hz slow waves were higher in Group E than in Group U, and therefore they were related to epileptogenicity, and the presence of vHFO2 had the highest OR (3.245 [95 % CI 2.034–5.445]). In contrast, the coupling rate of FRs with the trough–peak transition of 0.5–1 Hz and 1–2 Hz slow waves was lower in Group E than in Group U, and it was hence related unlikely to epileptogenicity. It was of note that the rate of ascending phase of 3–4 Hz and 4–8 Hz slow waves was generally low (corresponding rate 13.3–46.1 %) and that the rate of FR coupling with trough–peak transition of 0.5–1 Hz and 1–2 Hz slow waves was generally high (corresponding rate 52.5–88.8 %).

In multivariate logistic regression analysis, FR power, the concurrent presence of spike and vHFO2, and FR coupling with the trough–peak transition of 3–4 Hz and 4–8 Hz slow waves were significantly positively associated with epileptogenicity. Among these, the concurrent presence of spike and vHFO2 and FR coupling with the trough–peak transition of 3–4 Hz and 4–8 Hz slow waves had higher OR (2.266 [95 % CI 1.435–3.574], 2.323 [1.356–4.144], 2.726 [1.713–4.453], and 2.261 [1.556–3.321], respectively) than the other parameters (Table 3). Conversely, FR coupling with the trough–peak transition of 0.5–1 Hz and 1–2 Hz slow waves was negatively associated with epileptogenicity.

4. Discussion

4.1. Significance of very high-frequency oscillations

This study suggests that FRs accompanied by spikes and/or vHFOs above 600 Hz are more likely to be epileptogenic. In particular, vHFOs above 600 Hz were observed in 20.8 % of Group E but in only 8.3 % of Group U. The presence of vHFOs above 600 Hz is considered to be important in considering epileptogenicity, although their overall detection rate was rather limited. Conversely, there was no difference between the two groups in the coexistence of vHFOs of 500–600 Hz. FRs are often defined as up to 600 Hz, so there seems to be little significance in evaluating HFOs of 500–600 Hz separately. Although Usui et al. and

Table 2
Univariate analysis to predict epileptogenicity.

Parameter	Group E (%)	Group U (%)	Odds ratio	95 % CI	p
FR					
Frequency	294.1 (250.2–469.9)†	299.0 (250.2–465.0)†	0.996	0.993–0.998	< 0.001
Log-power	−0.3 (−8.6–13.2)†	−3.0 (−9.4–6.9)†	1.248	1.189–1.312	< 0.001
Concurrent activity of FR					
Spike	635 (88.4)	189 (78.4)	2.105	1.430–3.078	< 0.001
Ripple	241 (33.6)	58 (24.1)	1.594	1.148–2.239	0.006
vHFO1	151 (21.0)	41 (17.0)	1.299	0.895–1.920	0.18
vHFO2	163 (22.7)	20 (8.3)	3.245	2.034–5.445	< 0.001
Phase of slow activity (trough–peak transition)					
0.5–1 Hz	488 (68.0)	214 (88.8)	0.268	0.171–0.405	< 0.001
1–2 Hz	377 (52.5)	172 (71.4)	0.444	0.322–0.606	< 0.001
2–3 Hz	206 (28.7)	57 (23.7)	1.299	0.931–1.833	0.13
3–4 Hz	201 (28.0)	32 (13.3)	2.539	1.713–3.870	< 0.001
4–8 Hz	331 (46.1)	58 (24.1)	2.699	1.951–3.777	< 0.001

CI, confidence interval; FR, fast ripple; vHFO, very-high-frequency oscillation.
†: Median (range).

Table 3
Multivariate logistic regression analysis to predict epileptogenicity.

	Odds ratio	95 % confidence interval		Wald test *p*
		Lower	Upper	
(Intercept)	1.987	0.631	6.254	0.24
FR				
Frequency	1.002	0.999	1.006	0.12
Log-power	1.253	1.187	1.326	< 0.001
Concurrent activity of FR				
Spike	2.266	1.435	3.574	< 0.001
vHFO1	0.629	0.394	1.010	0.05
vHFO2	2.323	1.356	4.144	0.003
Phase of slow activity (trough–peak transition)				
0.5–1 Hz	0.382	0.234	0.607	< 0.001
1–2 Hz	0.499	0.347	0.712	< 0.001
3–4 Hz	2.726	1.713	4.453	< 0.001
4–8 Hz	2.261	1.556	3.321	< 0.001

Model chi-squared test $p < 0.001$.
Hosmer–Lemeshow test $p = 0.71$.
FR, fast ripple; vHFO, very-high-frequency oscillation.

Brázdil et al. mentioned the usefulness of vHFOs above 1,000 Hz when considering the epileptogenic zone [10,11], vHFOs of 600–1200 Hz are also indicated to be more specific biomarkers of epileptogenicity than FRs alone in the present study.

The precise mechanism of vHFO generation has not yet been elucidated. Even in epileptic neurons, the rate of action potential firing is often limited to < 300 Hz [24]. One hypothesis about the mechanism behind FRs and vHFOs, which have frequencies exceeding the physiological limit of neuronal firing, is that they are not caused by the oscillations of a single synchronized group of neurons but by the overlapping of out-of-phase oscillations of multiple asynchronous neuronal groups [7,11]. This strong disruption of synchrony may indicate strong epileptogenic potential.

4.2. Significance of phase of slow waves coupled with fast ripples

Sleep slow waves (0.5–4 Hz) can reflect the periodic switch of cortical neuronal excitability between the up (activated) and down (deactivated) states in the brain and are shown to influence physiological brain rhythms [25,26]. Frauscher et al. reported that HFO (80–250 Hz) density in channels with epileptic activity was highest during the transition between the negative peak and the preceding positive phase of slow waves (i.e., from the 'up' state to the 'down' state), while HFO density in channels with normal activity increased during the period from the negative peak ('down' state) to the following positive phase ('up' state) [5]. Song et al. demonstrated that, in the frontal and parietal lobes, the incidence rate for the ripples occurring during the trough–peak transition of slow, theta, and other waves was significantly increased in the SOZ compared with the non-SOZ in intracranial EEG [27]. In the study by Amiri et al. regarding the phase of coupling between theta waves and FRs, the rate of FRs in the trough–peak transition was higher in the SOZ than in non-SOZ, while this rate in the peak–-trough transition was higher in non-SOZ [17]. Coupling with 3–4 Hz delta waves is believed to be related to epileptogenicity [16,18,28]. Studies of PAC analysis of intracranial ictal EEG have also reported strong coupling between HFOs and 4–8 Hz theta band waves [29,30]. Our findings of the occurrence of epileptic FRs in the trough–peak transitions of 3–4 Hz and 4–8 Hz slow waves were in accordance with these reports. Regarding the 0.5–1 Hz slow wave coupling, which is considered to have a weak relation with epileptogenicity, the FR rate in the trough–peak transition was lower in the EAs than in the unlikely EAs, suggesting that FRs coupled with slow waves in this frequency range are actually close to non-epileptic ones. However, there are several unclarified issues about FR-slow wave coupling: why highly epileptogenic HFOs tend to couple with 3–4 Hz slow waves; what neuronal activity is reflected by the HFO-coupling of trough–peak and peak–trough transition; why the rate of FRs coupled with the trough–peak transition was generally high in slow waves < 2 Hz and low in other waves. Further investigation is needed to determine whether the coupling phase can really be an indicator of epileptogenicity.

The amplitude of associated slow activity was not too low to cause a computational error in any FR in this study. However, a definition of the lower limit of such a slow wave amplitude may be needed to ensure the accuracy of phase estimations in future studies.

4.3. Significance of findings

In epilepsy resection surgery, it is important to fully resect the epileptogenic zone in order to achieve a complete cure of seizures [31]. The occurrence rate of FRs is well known as an epileptogenic marker. In this study, some electrodes in the EA showed a relatively high rate of FRs, but this tendency was not consistent across patients. There are various indicators of epileptogenicity, such as epileptic discharges, HFOs, and PACs, and FRs are particularly important, but individual indicators alone are insufficient. We consider that the significance of FRs as epileptogenicity will be enhanced by checking multiple coexisting indicators of epileptogenicity in addition to FRs themselves. Among them, the power of FRs, simultaneous epileptic discharges and vHFOs above 600 Hz, and coupling phase with slow waves of each frequency band are important, and the presence of multiple indicators of these may be linked to the strength of epileptogenicity. We hope that these analyses will lead to better outcomes in resection surgery.

4.4. Limitations

We are aware of several limitations in this study. First, three electrodes were selected from both the EA and unlikely EA in each patient for comparison. This selection of electrodes was based on subjective decisions to some extent, and the results might be somewhat biased. Second, a large number of FRs were automatically detected from each electrode of each patient, but a considerable number of artifacts and other activities were mistakenly included and rejected by the reviewers. We need to develop an artifact rejection method to solve this issue, but this will be another demanding future project. The number of identified true FRs varied widely among patients. In particular, many of the FRs detected from the unlikely EA were judged as false FRs and were excluded from the analysis. Those judged as true FRs and recorded from the unlikely EA were observed in only five patients. Third, we did not analyze the occurrence rate of FRs in a fixed recording duration, which is also thought to be related to epileptogenicity because of our methodology to automatically detect the first 100 candidate FRs. Fourth, cortical and depth electrodes were not separated in the analysis. There is the possibility that the power coupling phase and other parameters of the detected FRs may differ depending on the electrode type. The fifth limitation was that there were some electrodes in the brain regions that were unlikely to be epileptogenic but had to be resected in the surgical procedure in two patients. There were no other possibly "unlikely EA" electrodes in the limited set of 37 electrodes remaining in the EEG system with 5 kHz sampling in these patients because the non-resected regions covered by the limited electrodes appeared partly epileptogenic. Therefore, we refrained from using the term "non-epileptogenic area" in this study. We hope in the future to compare EEG data between EA and truly non-epileptogenic areas involving a full set of electrodes with 5 kHz sampling.

5. Conclusions

We detected FR-related factors that were highly associated with epileptogenicity through a multivariate logistic regression analysis. Considering that epileptogenicity indicated by FRs may be reinforced by

the simultaneous occurrence of spikes and vHFOs above 600 Hz and the phase of FR-slow wave coupling, we hope our findings will lead to the development of a multi-factorial analytic tool involving FRs and these related parameters would precisely predict epileptogenicity for improvement of treatment outcomes in epilepsy surgery. The next challenge will be to verify prospectively whether our method is applicable to new cases.

Funding information

T. Shibata was supported by the Japan Epilepsy Research Foundation (Grant Number JERF TENKAN 22005).

2.4. Ethics

This study was approved by the Okayama University Ethics Committee (Ken #2109-029).

CRediT authorship contribution statement

Takashi Shibata: Writing – original draft, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Hiroki Tsuchiya:** Writing – review & editing, Investigation. **Mari Akiyama:** Writing – review & editing. **Tomoyuki Akiyama:** Writing – review & editing. **Masao Matsuhashi:** Writing – review & editing, Software. **Katsuhiro Kobayashi:** Writing – review & editing, Validation, Supervision, Software, Methodology, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: [M. Matsuhashi belongs to the Department of Epilepsy, Movement Disorders and Physiology, Kyoto University, which is the Industry-Academia Collaboration Courses, supported by Sumitomo Pharma Co., Ltd. and Nihon-Kohden Corporation].

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