

High-frequency Oscillations and the Seizure Onset Zones in Neocortical Epilepsy

Yan-Ping Sun^{1,2}, Yu-Ping Wang^{1,3}, Zhi-Hong Wang², Feng-Yu Wu⁴, Li-Ou Tang², Shou-Wen Zhang^{1,5}, Hai-Tao Pei², Yan Wang², Zhao-Yang Huang¹, Qing Xue¹, Cui-Ping Xu⁶, Jun-Li Tai⁷

¹Department of Neurology, Xuanwu Hospital, Capital Medical University, Beijing 100053, China

²Department of Neurology, The Affiliated Hospital of Qingdao University, Qingdao, Shandong 266003, China

³Beijing Key Laboratory of Neuromodulation, Beijing 100053, China

⁴Department of Radiology, The Affiliated Hospital of Qingdao University, Qingdao, Shandong 266003, China

⁵Epilepsy Department, Beijing Chaoyang Emergency Hospital, Beijing 101149, China

⁶Beijing Institute of Functional Neurosurgery, Xuanwu Hospital, Capital Medical University, Beijing 100053, China

⁷Department of Functional Neurosurgery, Beijing Luhe Hospital, Capital Medical University, Beijing 100122, China

Abstract

Background: To study the characters of high-frequency oscillations (HFOs) in the seizure onset zones (SOZ) and the nonseizure onset zones (NSOZ) in the electrocorticography (ECoG) of patients with neocortical epilepsy.

Methods: Only patients with neocortical epilepsy who were seizure-free after surgery as determined with ECoG were included. We selected patients with normal magnetic resonance imaging before surgery in order to avoid the influence of HFOs by other lesions. Three minutes preictal and 10 min interictal ECoG as recorded in 39 channels in the SOZ and 256 channels in the NSOZ were analyzed. Ripples and fast ripples (FRs) were analyzed by Advanced Source Analysis software (ASA, The Netherlands). Average duration of HFOs was analyzed in SOZ and NSOZ separately.

Results: For ripples, the permillage time occupied by HFOs was 0.83 in NSOZ and 1.17 in SOZ during the interictal period. During preictal period, they were 2.02 in NSOZ and 7.93 in SOZ. For FRs, the permillage time occupied by HFOs was 0.02 in NSOZ and 0.42 in SOZ during the interictal period. During preictal period, they were 0.03 in NSOZ and 2 in SOZ.

Conclusions: High-frequency oscillations are linked to SOZ in neocortical epilepsy. Our study demonstrates the prevalent occurrence of HFOs in SOZ. More and more burst of HFOs, especially FRs, means the onset of seizures.

Key words: Electrocorticography; Epilepsy; High-frequency Oscillations; Seizure Onset Zones

INTRODUCTION

Epileptic high-frequency activity includes pathological activities with frequency above 80 Hz recorded in epileptic brains *in vitro*, in animal models and in patients.^[1] Isolated high-frequency oscillatory events are the most common type of high-frequency activity and are called high-frequency oscillations (HFOs).^[1] HFOs include ripples (80–250 Hz) and fast ripples (FRs) (250–500 Hz).^[2,3] Different studies use slightly different frequency bands. Only events containing at least 4 consecutive oscillations above 80 Hz were regarded as HFOs.^[1] It has been proposed that HFOs are related to the epileptic attack by animal trial.^[4,5] Recent studies suggest the changes of HFOs in epileptic brains are related to epileptogenesis and seizure genesis.^[6]

The characteristics of HFOs in mesial temporal epileptic patients during ictal and interictal periods have been well studied. Our study focused on neocortical epileptic patients who were seizure-free after surgery with normal magnetic resonance imaging (MRI) before surgery avoiding the influence of HFOs by other lesions. The seizure onset zones (SOZ) of the patients should be verified by the consequences of surgery. The removal of areas with HFOs seems to predict effective surgical interventions.^[7,8]

METHODS

Selection of patients

Between December 2010 and January 2012, 18 patients with implanted subdural electrodes for epilepsy surgery evaluation were recorded at a sampling rate of 1600 Hz in our epilepsy center. Patients with a proven neocortical epilepsy and normal MRI before surgery were included in this study.

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Address for correspondence: Prof. Yu-Ping Wang,
Department of Neurology, Xuanwu Hospital,
Capital Medical University, Beijing 100053, China
E-Mail: wangyuping01@sina.cn

Besides, We only selected patients that were seizure-free for more than 1-year after surgery. The details of the patients are listed in Table 1. Other patients were excluded because of three reasons: Abnormal MRI before surgery, still with seizures after surgery, not neocortical epilepsy.

Electrocorticography recording

Patients were implanted subdural electrodes according to clinical history, seizure semiology and surface electroencephalogram (EEG) investigations. The electrodes have a 2.5 mm stainless steel central core, with a 10 mm interconnecting distance. The ECoG was sampled by a 128-channel Grass/Twins Monitoring System (Grass Technologies, USA) at the sampling rate of 1600 Hz with low-frequency cut of 0.1 Hz and high-frequency cut of 500 Hz. The ECoG was recorded for 3–14 days constantly in order to acquire at least three seizures to orient the epileptogenic zone. The data were visually inspected, and channels with artifacts were removed. In total, at last 295 channels of the ECoG were analyzed.

High-frequency oscillations analysis

Ten minutes ECoG data during interictal periods were selected. Interictal data imply that there was no seizure within 1 h before and after the selected section for each individual patient. For preictal period, 3 min data were selected. The ECoG data were transformed to European Data Format form in order to be read by the analysis software. Ripples and FRs were analyzed by Advanced Source Analysis (ASA) (ASA, The Netherlands) software. At last, 295 channels were analyzed including 39 channels from SOZ and 256 channels from nonseizure onset zones (NSOZ). The SOZ was identified as the area showing the earliest EEG change (ictal discharge) from baseline prior to or concomitant with clinical onset.^[9] Ripples were analyzed with a filter from 80 to 250 Hz at the computer screen resolution ratio 1280 (0.8 s/page, 100 μ V/cm). FRs were analyzed with 250 and 500 Hz filters at the computer screen resolution ratio 1280 (0.5 s/page, 30 μ V/cm). The accurate starting and ending point and the numbers of HFOs can be read from the ASA [Figure 1]. The duration of every oscillation can be calculated by the starting and ending time. Permillage time occupied by HFOs can be calculated then.

Statistical analysis of average duration of high-frequency oscillations

Multiple comparison of rank sum test was used to compare the average duration of ripples and FRs inside and outside the SOZ. Statistical significance was set at $P < 0.05$.

RESULTS

The results of ripples and FRs are listed in Tables 2 and 3.

The average duration of ripples

The average duration of every ripple in the SOZ was longer than that in the NSOZ during interictal periods ($Z = 6.94$, $P < 0.001$). During the preictal periods, there was no different between in SOZ and NSOZ ($Z = 1.44$, $P = 0.075$).

The average duration of fast ripples

The average duration of every FRs inside the SOZ were shorter than that outside the SOZ during both interictal ($Z = 7.16$, $P < 0.001$) and preictal periods ($Z = 2.35$, $P = 0.009$). During interictal period, the PT of FRs in SOZ is more than 20 times than that in NSOZ. And during the preictal period, the PT of FRs in SOZ is about 67 times than that in NSOZ.

Permillage time occupied by ripples

For ripples, the permillage time occupied by HFOs was 0.83 in NSOZ and 1.17 in SOZ during the interictal period. During preictal period, they were 2.02 in NSOZ and 7.93 in SOZ.

Permillage time occupied by fast ripples

For FRs, the permillage time occupied by HFOs was 0.02 in NSOZ and 0.42 in SOZ during the interictal period. During preictal period, they were 0.03 in NSOZ and 2 in SOZ.

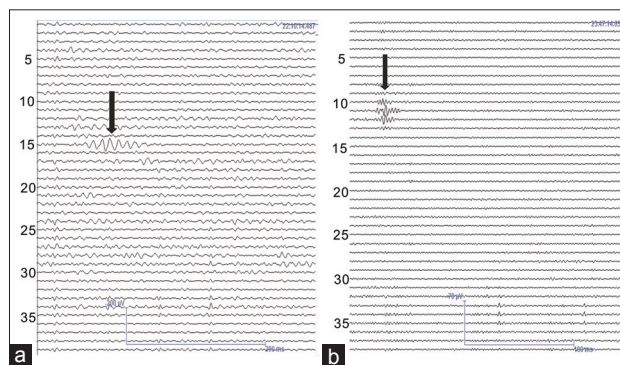


Figure 1: Ripple (a) and fast ripple (b) analyzed by Advanced Source Analysis.

Table 1: Clinical and electrophysiological data of four patients

Patient	Age (years)/gender	History of epilepsy before surgery (years)	AEDs ever tried	Seizure frequency before surgery	Electrode positions	Electrode numbers	Surgery site
1	7/male	2	VPA, CBZ, LTG	3-4/day	BF, BT	80	R-SMF
2	19/male	14	VPA, CBZ	2-3/day	LF, LT, LP	76	L-MIF
3	16/male	4	VPA, CBZ, TPM, LEV	1-2/month	RF, RT	96	R-PNT
4	21/male	18	CBZ, LTG, VPA, OXC, TPM	1/week	LF, LT	64	L-DF

VPA: Sodium valproate; CBZ: Carbamazepine; LTG: Lamotrigine; TPM: Topiramate; LEV: Levetiracetam; OXC: Oxcarbazepine; B: Bilateral; L: Left; R: Right; F: Frontal lobe; T: Temporal lobe; P: Parietal lobe; SMF: Superior and middle frontal gyrus; MIF: Middle and inferior frontal gyrus; PNT: Posterior of neocortical temporal lobe; DF: Dorsolateral frontal lobe; AED: Anti-epileptic drug.

Table 2: Result of ripples

Period	Area	AD (ms)	PT
Interictal	SOZ	83.64 ± 42.41	1.17
	NSOZ	67.59 ± 27.16	0.83
Preictal	SOZ	138.16 ± 92.06	7.93
	NSOZ	133.02 ± 87.62	2.02

AD: The average duration of HFO; PT: The permillage time occupied by HFOs; SOZ: Seizure onset zones; NSOZ: Nonseizure onset zones; HFOs: High-frequency oscillations.

Table 3: Result of FRs

Period	Area	AD (ms)	PT
Interictal	SOZ	25.04 ± 13.66	0.42
	NSOZ	33.69 ± 12.36	0.02
Preictal	SOZ	23.25 ± 10.28	2
	NSOZ	29.14 ± 16.23	0.03

AD: The average duration of HFOs; PT: The permillage time occupied by HFOs; FRs: Fast ripples; SOZ: Seizure onset zones; NSOZ: Nonseizure onset zones; HFOs: High-frequency oscillations.

DISCUSSION

Multiple studies have investigated characteristics of HFOs in mesial temporal epileptic patients.^[10,11] Our results indicate that HFOs links to SOZ in patients with neocortical epilepsy without a visible lesion on MRI. The study selected patients with normal MRI in order to avoid the influence of HFOs by other lesions. All our patients were seizure-free proved that the removed areas included the epileptogenic tissue.

The percentage of occupancy by HFOs in the SOZ-channels was significantly higher than that in the NSOZ-channels. This increase was seen in ripples and FRs, especially FRs. During interictal period, the PT of FRs in SOZ is more than 20 times than that in NSOZ. And during the preictal period, the PT of FRs in SOZ is about 67 times than that in NSOZ. This result is consistent with other study.^[1] Nevertheless, the percentage of time occupied by HFOs in this study is less than Zijlmans' study.^[1] Perhaps there are three reasons. First, the patients in our study all have a normal MRI. Lesions may increase the incidence of HFOs. Second, Zijlmans selected 10 s before seizure onset while we analyzed 3 m before seizure onset and HFOs tend to increase before seizure onset. Third, Zijlmans chose chronic sleep stage as the interictal period that usually showed more epileptiform discharge in patients. Although FRs have been more strongly linked to epileptogenesis than ripples,^[7,12,13] we found that both were increased in the SOZ.

The percentage of occupancy by HFOs in the SOZ-channels was significantly higher than that in the NSOZ-channels, especially FRs. It indicates that FRs links to SOZ more closely than ripples. FRs proved to be a reliable epileptogenic marker since they were closely related to SOZ. Ripples are considered to play an important role in information processing, and consolidation of memory, which are thought as physiological HFO^[14-16] The distinction between physiological and pathological HFO has remained

unclear.^[15,17] Recently, it was showed that pathological HFO had higher mean spectral amplitude, longer mean duration, and lower mean frequency than physiological-induced HFO.^[18,19]

Perhaps there are different mechanisms for ripple and FRs in epilepsy.^[2,20] FRs represent field potentials of population spikes from clusters of abnormal synchronously bursting neurons, in contrast to ripples, which represent field potentials of summated inhibitory postsynaptic potentials.^[21] The average duration of every FRs was shorter in SOZ than in NSOZ during both interictal and preictal period. Maybe neurons producing the FRs focused on a limited area may cause shorter average duration in the SOZ.

Seizure onset zone is the area where a seizure originates.^[22] HFOs are related to epilepsy. More and more burst of HFOs, especially FRs, means the onset of seizures. HFOs, especially FRs are linked to SOZ in neocortical epilepsy.

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