Clin Neurophysiol. Author manuscript; available in PMC 2013 September 12.

Published in final edited form as:
Clin Neurophysiol. 2011 April ; 122(4): 664–671. doi:10.1016/j.clinph.2010.09.021.

Ictal and interictal high frequency oscillations in patients with focal epilepsy

Maeike Zijlmans[a,b,*], **Julia Jacobs**[a], **Yusuf U. Kahn**[a], **Rina Zelmann**[a], **François Dubeau**[a], and **Jean Gotman**[a]

[a]Montreal Neurological Institute and Hospital, McGill University, Montreal (Québec), Canada
[b]University Medical Center Utrecht, The Netherlands

Abstract

Objective—High frequency oscillations (HFOs) can be recorded with depth electrodes in focal epilepsy patients. They occur during seizures and interictally and seem important in seizure genesis. We investigated whether interictal and ictal HFOs occur in the same regions and how they relate to epileptiform spikes.

Methods—In 25 patients, spikes, ripples (80–250 Hz) and fast ripples (FR: 250–500 Hz) and their co-occurrences were marked during interictal slow wave sleep (5–10 min), during 10 preictal seconds and 5 s following seizure onset. We compared occurrence and spatial distribution between these periods.

Results—HFOs and spikes increased from interictal to ictal periods: the percentage of time occupied by ripples increased from 2.3% to 6.5%, FR from 0.2% to 0.8%, spikes from 1.1% to 4.8%. HFOs increased from interictal to preictal periods in contrast to spikes. Spikes were in different channels in the interictal, preictal and ictal periods whereas HFOs largely remained in the same channels.

Conclusions—HFOs remain confined to the same, possibly epileptogenic, area, during interictal and ictal periods, while spikes are more widespread during seizures than interictally.

Significance—Ictal and interictal HFOs represent the same (epileptogenic) area and are probably similar phenomena.

Keywords

High frequency oscillations; Focal epilepsy; Epilepsy surgery; Depth EEG; Ictogenesis

1. Introduction

High frequency oscillations (HFOs) occur in patients with focal epilepsy, mostly during slow wave sleep and at seizure onset (Bagshaw et al., 2009; Bragin et al., 1999b, 2002; Fisher et

*Corresponding author at: University Medical Center Utrecht, Neurology, Hp F02.230, Heidelberglaan 100, 3584 CX Utrecht, The Netherlands. Tel.: +31 (0)88 7553496; fax: +31 (0)30 2542100. g.j.m.zijlmans@umcutrecht.nl (M. Zijlmans).

There are no conflicts of interest.

al., 1992; Jirsch et al., 2006; Khosravani et al., 2009; Urrestarazu et al., 2007). They have been associated with epileptogenesis as they occur before the first seizure in the kainic acid rat model (Bragin et al., 2004a). HFOs appear to co-localize with the seizure onset zone (SOZ), which suggests that they are involved in seizure genesis (Bragin et al., 2004b; Jacobs et al., 2008). Interictal HFOs increase after medication reduction in parallel with the increase in seizure frequency, indicating that the amount of interictal HFOs mirror the level of disease activity (seizure frequency) (Zijlmans et al., 2009). HFOs seem better markers for the SOZ than epileptic spikes and do not depend on the underlying pathology (Jacobs et al., 2008, 2009a). Finally, removal of HFO generating tissue is related to good surgical outcome, more than spikes and the SOZ are (Jacobs et al., 2010), which supports their relation to epileptogenic tissue and potential clinical importance. The current hypothesis is that HFOs result from misconnected or disinhibited neuronal networks leading to highly synchronized neuronal activity over an area of brain tissue, which in turn results in seizure genesis after other areas or networks get involved (Bragin et al., 2004a; Engel et al., 2009; Ogren et al., 2009).

HFOs can be divided into ripples (80–250 Hz) and fast ripples (FRs: 250–500 Hz) (Bragin et al., 1999a; Staba et al., 2002; Urrestarazu et al., 2007). Ripples have been thought to be more physiological in nature and involved in memory, while FRs appear to be pathological, except for FRs in sensory evoked potentials (Axmacher et al., 2008; Buzsaki et al., 1992; Curio et al., 1997; Engel et al., 2009; Worrell et al., 2008). HFOs often co-occur with epileptic spikes, but there are HFOs without spikes and spikes without HFOs (Jacobs et al., 2008; Urrestarazu et al., 2006). They appear to represent a different epileptic phenomenon than spikes, as interictal HFOs respond to medication change in a different way than interictal spikes (Zijlmans et al., 2009).

It has been suggested that HFOs increase pre-ictally and that seizures arise when a certain tipping point is reached. The amount of high frequencies increases a few seconds before seizure onset (Jirsch et al., 2006; Khosravani et al., 2009). However, it is uncertain whether there is a change during the minutes preceding seizure onset (Jacobs et al., 2009b).

Interictal and ictal HFOs have been studied separately (Crepon et al., 2010; Jacobs et al., 2008; Jirsch et al., 2006). In this study we want to assess how the interictal HFOs relate to ictal HFOs for rates and spatial distribution, and how this compares to the immediate pre-ictal period. Similar comparisons will be made for interictal spikes. Knowledge of these relations can improve the understanding of the pathophysiology of seizures and the meaning of HFOs in epilepsy.

2. Methods

2.1. Patient selection

Between September 2004 and September 2007, 42 patients with medically intractable focal epilepsy underwent intracranial depth stereo-EEG (SEEG) investigations. We selected patients who had 10 min of interictal slow wave sleep with no seizure within two hours, with one predominant seizure onset type (more than 80% of their seizures) and at least one seizure that represented the patient’s habitual seizure pattern recorded at 2000 Hz with few

artifacts (no more than one quarter of channels), thus allowing the study of both interictal and ictal HFOs. The Montreal Neurological Institute and Hospital Research Ethics Committee approved the study and informed consent was obtained from all patients.

2.2. SEEG recordings

Patients were monitored with video-SEEG during 10–21 days, and recorded with a 128-channel Harmonie monitoring system (Stellate, Montreal, Canada). During part of the monitoring session, SEEG was acquired with a 500 Hz low-pass hardware filter and a sampling rate of 2000 Hz. The intracerebral electrodes were manufactured on site by wrapping a 0.254 mm stainless steel central core with 0.076 mm stainless steel wire, coated with Teflon and stripped focally yielding electrode contacts. The electrode tip formed the deepest contact (1 mm length; effective surface 0.85 mm^2) and the other eight contacts were 5 mm apart (0.5 mm; 0.80 mm^2). Electrode placement resulted from clinical decisions. Typically, three temporal depth electrodes were directed orthogonally through the middle temporal gyrus with the deepest contacts in the amygdala, anterior hippocampus and parahippocampal gyrus. Numbers of electrodes for extra-temporal lobe structures varied and direction depended on the target region and the vasculature (see also Table 1).

2.3. Marking interictal HFOs and spikes

Only a few nights per patient were recorded at 2000 Hz, mostly during the beginning of the recording. We selected the first night recorded at 2000 Hz with co-registered EMG and EOG channels. After spectral analysis of an EMG channel for muscle activity and a non-spiking SEEG channel for delta activity, 10 min of slow wave sleep (more than 25% delta) at least 10 h away from any seizure were selected.

EEG-analysis software (Harmonie reviewer, Stellate, Montreal) was used. The selected EEGs were reviewed in bipolar montage by two observers (MZ, JJ) to minimize subjectivity and to split the workload. For all patients, both observers marked 1 min. Then, inter-observer agreement was calculated using Cohen's kappa coefficient. Channels with kappa below 0.5 were reviewed jointly by both reviewers and a consensus was reached on how to mark the events. Then, one reviewer was assigned randomly and this reviewer marked 5 min according to the consensus. The stability of events in these 5 min was determined and if instability was detected, five additional minutes were marked (Zelmann et al., 2009). HFOs were marked using a vertically split screen with an 80 Hz high-pass filter on the left and a 250 Hz high-pass filter on the right to distinguish ripples from FRs. The time scale was set to maximal resolution (0.8 s/page on a 48 cm width monitor) and the amplitude scale was raised to 1 μV/mm. An event was considered a ripple or FR if it was clearly above baseline and consisted of at least four consecutive oscillations. A ripple was marked if an event was clearly visible on the side of the 80 Hz filter and not on the 250 Hz, while a FR was marked if visible on the side of the 250 Hz filter. An illustration of the procedure is given in the Supplementary Material S1; also available at http://apps.mni.mcgill.ca/research/gotman/2000HZ.html. Spikes were reviewed on a separate copy of the EEG displayed with standard parameters (0.3–70 Hz filter, 10 s/page, 30 μV/mm). All channels were reviewed and analyzed, except channels that were outside the brain, non-functional or showing artefacts.

2.4. Marking HFOs and spikes during and before seizures

We selected one seizure per patient according to the following criteria: (1) recorded at 2000 Hz, (2) representative for the patient's habitual seizures, (3) closest to the analyzed interictal night, (4) with a well defined time of seizure onset in the EEG report and (5) without artifacts on the seizure onset channels during the epochs marked. Because the night selected for interictal data was often one of the first nights of recording, while seizures sometimes started later, the selected night and seizure could be several days apart. The electrographic onset, defined as sustained rhythmic discharges which cannot be explained by physiological changes or state changes and which resulted in the habitual clinical seizures (Gotman et al., 1993), was derived from the clinical EEG report and evaluated by the authors (MZ, JJ, filter 0.3–70 Hz). When the rhythmic discharge was preceded by a change in spikes, as can be seen in mesiotemporal epilepsy, the onset rhythmic discharge was taken as the seizure onset (Lee et al., 2000). This moment was marked within the EEG, as well as 10 s before the first EEG change and 5 s after the first EEG change. All channels were assessed for muscle artifact, which can be present in SEEG (in the superficial electrode contacts), by reviewing at normal time scale (10 s/page), with a normal and with an 80 Hz high-pass filter and amplitude of 1 μV/mm together with the epidural and EMG/EKG channels. Muscle artifacts are well recognizable as they occur simultaneously over the involved channels, mostly on the outer channels of the depth electrodes (Fig. 1). Also, although they contain similar frequencies as HFOs, they have a frequency spectrum that is slightly different giving them a different appearance (Otsubo et al., 2008). These channels were excluded from the analysis as were channels known to be outside the brain or nonfunctional.

The EEG between 10 s before the electrographic onset until 5 s after the electrographic onset was reviewed for spikes (10 s/page, 0.3–70 Hz, 30 μV/mm). Waves having the morphology normally attributed to interictal spikes were considered as ictal spikes if they occurred during the ictal period. A train of rhythmic (ictal) spikes adjacent to each other was marked as one polyspike. Then, the EEG was reviewed for ripples and FRs similarly to the interictal EEG (0.8 s/page, split screen with 80 and 250 Hz filters, 1 μV/mm). The reviewer was not blinded for whether data were interictal, pre-ictal or ictal, as this could be deducted from the epoch lengths. However, given that data were reviewed with the above characteristics, the reviewer did not see in which channels there was actual seizure activity at the usual time scale with frequencies below 80 Hz. The SOZ was derived from the clinical EEG report by two authors (MZ, JJ) and defined as the channels containing sustained non-physiological rhythmic discharges (with filter 0.3–70 Hz) during the first 5 s of the seizure. Whenever there was doubt, the EEGs and reports were discussed with the clinical neurophysiologist (FD).

2.5. Analysis

From the marker files, a MATLAB program calculated the rates and duration of spikes, ripples and FRs and their overlap per channel for the 5–10 min of interictal slow-wave-sleep, the 10 pre-ictal seconds and the first 5 s after seizure onset. Not only the rates, but also the amount of time occupied by the different events (rate multiplied by mean duration) was calculated. For most comparisons, the percentage of time that a certain channel was

occupied by an HFO or spike was used instead of event rates, because ictal HFOs or spikes could be continuous and rates could therefore not always be calculated reliably.

2.6. Percentages of time

To study differences in event density between different periods (interictal, pre-ictal and ictal), the average percentage of time of all events (ripples, FRs, spikes, HFOs with and without spikes: R_Sp, FR_Sp, R_isol, FR_isol) were compared between interictal slow-wave-sleep (5 or 10 min), the 10 s pre-ictal period and the first 5 s after ictal onset, *averaged across channels*. Given the lack of normality of the data, we used a Kruskal–Wallis Test to compare interictal, pre-ictal and ictal periods for all channels, SOZ- and non-SOZ channels and the Tukey's honestly significant differences test to correct for multiple comparison ($p < 0.05$).

We tested whether there was a difference in percentage of time of events between SOZ and non-SOZ channels for each period, using a Wilcoxon rank sum test ($p < 0.05$), to see whether events occurred significantly more in the SOZ channels.

Finally, we studied which event in which state was the best to distinguish SOZ from non-SOZ channels. This was determined by calculating the ratio obtained by dividing the difference between the percentages of time per channel for the SOZ-channels and the non-SOZ channels by the sum of both: (SOZ + non-SOZ)/(SOZ + non-SOZ). An outcome of +1 would mean that events only occurred in the SOZ, while an outcome of −1 would mean events occurred only in channels outside the SOZ. Zero means there is no difference between SOZ and non-SOZ channels.

2.7. Changes over channels

In the above analysis, we examined together all channels or groups of channels (e.g. all channels or all channels in the SOZ). We also wanted to study whether interictal and ictal HFOs occurred in the same or in different channels to judge whether they represented the same event, and similarly for spikes. We used two ways to study this: (1) by calculating differences in the distribution of amounts of events over channels using a ranking distance; (2) by dividing channels into those with and without interictal events to see whether the ictal events occurred predominantly in the channels with or without interictal events.

2.7.1. Changes over channels – Ranking distance—To study whether the events occurred in the same channels interictally, pre-ictally and ictally, the channels are first ranked in each condition, from the channel with the highest percentage of time with an event to the channel with the lowest percentage of time with the same event. It is then possible to measure the "ranking distance" (RKD) between interictal, pre-ictal and ictal periods (Zelmann et al., 2009). The RKD measures the difference between two rankings by measuring how much the second ranking needs to be changed to become identical to the first (Fig. 2). For instance, if channel A is 2nd in the interictal ranking and 5th in the ictal ranking, the RKD of channel A between interictal and ictal periods is three. This value is then weighted by the difference in percentage of time occupied by events between the 2nd and the 5th position in the interictal ranking. This allows taking into account the fact that

there can be the same rank difference but large or small differences in value (Fig. 2). In other words, the RKD measures how much the distribution of events over channels differs between two periods of SEEG. This RKD was calculated between all three periods (ictal to interictal, ictal to pre-ictal and pre-ictal to interictal) for each patient.

Based upon our earlier experiences (Zelmann et al., 2009), we considered an RKD of more than 0.2 to be high. We studied whether the RKDs for all patients between ictal and interictal, ictal and pre-ictal and pre-ictal and interictal were higher than 0.2, using a *z*-test ($p = 0.05$).

2.7.2. Changes over channels – Interictal to ictal—We wanted to see whether changes over channels between interictal and ictal events (ripples, FRs, spikes) occurred mostly in the channels with or without interictal events. For this purpose we grouped channels into those with and without interictal events.

Channels with interictal rates below 0.2/s (less than one event per 5 s) were considered as having a rate of 0/s, since a rate below 0.2/s during the ictal period, which lasts 5 s, would yield zero events and therefore a zero rate. This allows a direct comparison of rates across epochs of varying durations.

We separated patients in whom all channels showed interictal event rates below 0.2/s and patients that showed no increase. For the remaining patients, channels were divided in two groups: (1) the channels with interictal rates above 0.2/s, “channels with interictal events” and (2) the channels with interictal rates below 0.2/s, “channels without interictal events”. We evaluated whether there was an increase of more than 2% per channel (e.g. percent of time with ripples going from 1% to 3%) compared to the interictal period and then evaluated in which group of channels this increase occurred predominantly (for spikes, ripples and FRs). Two percent is an arbitrary threshold which seemed reasonable because it represents appreciable change (being at least one event per 5 s).

3. Results

Twenty-five patients were included in the study, nine female, with an average age of 38 years (range: 23–51). Three patients had a previous resection. MR showed temporal atrophy in four patients, a disorder of migration in five, a porencephalic cyst in one and a central cyst in another, a vascular abnormality in two and no clear abnormalities in nine patients. Fourteen patients had a mesiotemporal seizure onset (see the Supplementary Table S1). In 21 of the 25 patients the selected interictal night preceded the seizure and the nights were on average 2.6 days away from the marked seizure. This means that between interictal and ictal periods, medication was overall tapered slightly. The implanted electrodes are given in Table 1. On average 32.1 channels (SD 10.1) were marked per patient, 4.8 (SD 3.7) of them being considered the SOZ. Seizure onset morphology could be divided into low-voltage fast activity in 22 patients and hypersynchronous high-amplitude EEG spikes (Spencer et al., 1992) in three.

3.1. Percentages of time with events

On average, 16.1 ripples, 2.5 FRs and 5.6 spikes per minute were marked per channel during interictal SEEG. Interictal SEEG was occupied on average per channel 2.3% of the time by ripples, 0.2% by FRs (13% of ripples and 33% of FRs overlapped with spikes) and 1.1% by spikes (Fig. 3). The *median* for all channels of percentage of time occupied by events is lower than 0.001%, because most channels contained zero events.

Pre-ictal SEEG was likewise occupied 3.9% of the time by ripples, 0.3% by FRs (8% and 13% overlap with spikes) and 0.9% by spikes. The ictal SEEG was occupied 6.5% of the time by ripples, 0.8% by FRs (34% and 40% overlap with spikes) and 4.8% by spikes (Fig. 3). Differences between the three periods were significant for ripples, FRs and spikes when all channels were considered together. There was an increase in ripples and FRs from interictal to pre-ictal and to ictal, and a decrease in spikes from interictal to pre-ictal with a high increase from pre-ictal to ictal (Kruskal–Wallis; $p < 0.05$). This trend was also seen when examining separately the channels within and outside the SOZ for the HFOs, with the following exceptions: the difference in ripples between interictal and pre-ictal was not significant for the SOZ channels; the FR increase from pre-ictal to ictal was not significant in the non-SOZ channels; for spikes, the decrease from interictal to pre-ictal was not seen in the SOZ channels.

The percentage of occupancy in the SOZ-channels was significantly higher than in the non-SOZ-channels for all events in all periods (Wilcoxon rank test; $p < 0.05$). The ratios between SOZ and non-SOZ channels are given in Table 2. The ratios were highest for the ictal period and for ripples.

As the results above indicate, most often there were more ictal HFOs than interictal HFOs. To give an idea of how common this increase was, we give the number of channels in which there was a large increase or decrease (more than 2%, e.g. a change in time occupied by HFOs from 1% to 3.5%). This increase was seen in SOZ channels as well as non-SOZ channels: an increase of more than 2% of time occupied with events between ictal and interictal periods was seen in 196 of 802 channels from 25 patients for ripples (84 of the 119 SOZ channels), 41 channels in 19 patients for FRs (25 of the 119 SOZ channels) and 181 channels in 21 patients for spikes (88 of the 119 SOZ channels). A decrease of more than 2% of time being occupied with events was seen in 39 of 802 channels from 11 patients for ripples (four SOZ channels), two channels in two patients (one SOZ channel) for FRs and 54 channels from 11 patients for spikes (five SOZ channels). The total of all events over all channels showed a decrease of more than 2% in three patients for ripples and spikes, and in none for FRs. One of the patients showing this decrease in ripples had an onset with hypersynchronous spikes.

3.2. Changes over channels – Ranking distance

The mean RKDs are given in Fig. 4. The RKDs were significantly higher than 0.2 for spikes between interictal, pre-ictal and ictal periods ($p < 0.05$), but they were not for ripples and FRs. In other words, the ranking of channels between interictal, pre-ictal and ictal differed for spikes, while the ranking of channels for ripples and FRs remained the same between

interictal, pre-ictal and ictal periods. This indicates that ictal HFOs occur in the same channels as interictal HFOs whereas spikes are distributed differently during the interictal, pre-ictal and ictal periods.

3.3. Changes over channels – Interictal to ictal

Which channels showed the greatest ictal increase: the channels with or without interictal events? This could be studied in 22 patients for ripples, 14 patients for FRs and 16 patients for spikes, as these patients had some channels with more than 0.2 interictal events per second and showed an ictal increase. For ripples, 17 of 22 patients showed greater increase in the channels with interictal ripples and five of 22 in channels without interictal ripples. For FRs, 12 of 14 patients showed a greater ictal increase in the channels with interictal FRs versus two of 14 patients in the channels without interictal FRs. For spikes, nine of 16 patients showed the highest ictal increase in the channels with interictal spikes versus seven of 16 patients showing a greater increase in the channels without interictal spikes. In other words, for all events the ictal increase occurs predominantly in the channels with interictal events, but spikes increase more often than HFOs in channels *without* interictal events. Fig. 5 shows summed bar graphs for all 25 patients after channels were divided into channels with and without interictal events. The figure shows that the increase in ictal spikes occurs over more channels, including channels with minimal interictal spikes and that the increases in spikes follow less clearly the interictal ranking than the ripples and FRs do.

4. Discussion

Most HFOs during the seizure onset occur in the same channels as interictal HFOs during slow wave sleep and during the pre-ictal period. This is not the case for spikes, which are more widespread and on different channels during seizures than interictally. Also, in contrast to spikes, HFOs increase pre-ictally. The amount of HFOs during the ictal period is higher than pre-ictally. This difference is similar in magnitude to the difference between the interictal and pre-ictal periods. This differs from spikes, which increase much more from the pre-ictal to the ictal period and show a reduction from the interictal to the pre-ictal period.

The occurrence of ripples and FRs in the same channels interictally and ictally suggests that interictal and ictal HFOs represent the same pathophysiological phenomenon and are the electro-graphic biomarker of the same epileptogenic tissue. The ripples were most related to the seizure onset zone in all states (interictal, pre-ictal and ictal). This strengthens the theory that HFOs might be seen as a local response within the epileptogenic area (Schevon et al., 2009). In the pre-ictal period, spikes are relatively rare compared to HFOs and compared to the period of interictal slow-wave sleep, but there is a steep increase of spikes over several channels after seizure onset. Also, there are important variations between patients and between channels in how the amount of spikes changes before seizures and during seizure onset. In contrast, HFOs steadily increase during the pre-ictal and ictal period and remain confined to few channels. Especially FRs never show a decrease. This can be understood if spikes indicate an (inhibitory) response to seizures, while HFOs represent focal epileptogenic tissue. Immediately preceding the seizure, inhibitory activity is reduced, which results in a reduction in spike activity, while the epileptogenic activity of the tissue

increases, which results in an increase in HFOs. Then, at seizure onset, larger circuits get involved, appearing as rhythmic activity over more channels (Bragin et al., 2005, 2007; Engel et al., 2009). Within these larger circuits the pathological tissue still oscillates at high frequencies, while in an adjacent but broader area spikes are seen. Within the epileptogenic tissue, interictal and ictal spikes often show co-occurring HFOs and so spikes seem to elicit HFOs, while in other regions ictal spikes occur without co-occurring HFOs. This suggests that wide areas in the brain can produce spikes during seizures, while only a small region produces HFOs.

There is an increase in the percentage of time with HFOs after seizure onset and some difference in distribution compared to the interictal period. This effect is smaller when considering only the HFOs without spikes. It has been suggested that HFOs with and without spikes represent different phenomena. For interictal HFOs it was found that HFOs co-occurring with spikes are longer in duration than HFOs without co-occurring spikes (Jacobs et al., 2008). Ictal HFOs are for a greater part related to spikes, so ictal HFOs might be longer in duration, explaining part of the effect.

We found a higher percentage of time occupied by HFOs shortly before seizure onset compared to the interictal period, which was most often recorded several nights before the seizure. This could be explained by an increase of HFOs just shortly before the seizure (Khosravani et al., 2009) or by an effect of reduction of the anti-epileptic medication between the interictal night and the pre-ictal period (Zijlmans et al., 2009). The increase between the interictal nights and the pre-ictal period is all the more striking because the interictal sample is from slow wave sleep, which in general contains more HFOs than wakefulness (Bagshaw et al., 2009), whereas the pre-ictal periods are often during wakefulness: on the basis of state alone, one would have expected a decrease in HFO rate.

In this study the ictal period was short. We decided to study only the first 5 s as this period was free of artifacts and because it allowed the study of the SOZ, defined on the same epoch. Discharge spread often took place some seconds after these 5 s. An alternative method would have been to extend the analysis until the spread of seizure activity rather than marking a defined time period. However, this spread is often gradual, not always easy to define and varies among patients. We believe that this would have introduced considerable variability between patients. Studying only 5 s did not introduce problems in calculating the amount of ripples and spikes. However, because FR rates are low, they were more difficult to estimate. The seizure onset was obtained from the clinical report, but it is well known that seizure onset can be gradual and difficult to determine exactly. (Mormann et al., 2007) This could influence the results, especially for the interpretation of the pre-ictal period. We reduced this potential bias by taking the very first suspected change as onset and leaving out seizures where the onset was unclear.

This study establishes a clear link between interictal and ictal HFOs, phenomena that were studied separately before. The pre-ictal HFO increase followed by a further ictal increase suggests a tight coupling between the generation of HFOs and of seizures. Ictal ripples are related to the seizure onset zone most and it could be clinically helpful to review seizure onsets also for higher frequencies. Experimental work would be required to assess whether

HFOs are causal to seizures or if the two phenomena are only tightly coupled without causality. Post-operative ECoG data could show whether removing tissue with HFOs actually lowers the amount of HFOs and how this relates to the clinical outcome.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was supported by grant MOP-10189 from the Canadian Institutes of Health Research and by the Netherlands Organization for Scientific Research (NWO) AGIKO-grant no. 92003481, the University Medical Center Utrecht (internationalization grant) and the “Stichting de drie lichten” (first author).

References

Axmacher N, Elger CE, Fell J. Ripples in the medial temporal lobe are relevant for human memory consolidation. Brain. 2008; 131:1806–17. [PubMed: 18503077]

Bagshaw AP, Jacobs J, LeVan P, Dubeau F, Gotman J. Effect of sleep stage on interictal high-frequency oscillations recorded from depth macroelectrodes in patients with focal epilepsy. Epilepsia. 2009; 50:617–28. [PubMed: 18801037]

Bragin A, Azizyan A, Almajano J, Wilson CL, Engel J Jr. Analysis of chronic seizure onsets after intrahippocampal kainic acid injection in freely moving rats. Epilepsia. 2005; 46:1592–8. [PubMed: 16190929]

Bragin A, Engel J Jr, Wilson CL, Fried I, Buzsaki G. High-frequency oscillations in human brain. Hippocampus. 1999a; 9:137–42. [PubMed: 10226774]

Bragin A, Engel J Jr, Wilson CL, Fried I, Mathern GW. Hippocampal and entorhinal cortex high-frequency oscillations (100–500 Hz) in human epileptic brain and in kainic acid-treated rats with chronic seizures. Epilepsia. 1999b; 40:127–37. [PubMed: 9952257]

Bragin A, Wilson CL, Almajano J, Mody I, Engel J Jr. High-frequency oscillations after status epilepticus: epileptogenesis and seizure genesis. Epilepsia. 2004a; 45:1017–23. [PubMed: 15329064]

Bragin A, Wilson CL, Engel J. Spatial stability over time of brain areas generating fast ripples in the epileptic rat. Epilepsia. 2004b; 44:1233–7.

Bragin A, Wilson CL, Engel J Jr. Voltage depth profiles of high-frequency oscillations after kainic acid-induced status epilepticus. Epilepsia. 2007; 48(Suppl 5):35–40.

Bragin A, Wilson CL, Staba RJ, Reddick M, Fried I, Engel J Jr. Interictal high-frequency oscillations (80–500 Hz) in the human epileptic brain: entorhinal cortex. Ann Neurol. 2002; 52:407–15. [PubMed: 12325068]

Buzsaki G, Horvath Z, Urioste R, Hetke J, Wise K. High-frequency network oscillation in the hippocampus. Science. 1992; 256:1025–7. [PubMed: 1589772]

Crepon B, Navarro V, Hasboun D, Clemenceau S, Martinerie J, Baulac M, et al. Mapping interictal oscillations greater than 200 Hz recorded with intracranial macroelectrodes in human epilepsy. Brain. 2010; 133:33–45. [PubMed: 19920064]

Curio G, Mackert BM, Burghoff M, Neumann J, Nolte G, Scherg M, et al. Somatotopic source arrangement of 600 Hz oscillatory magnetic fields at the human primary somatosensory hand cortex. Neurosci Lett. 1997; 234:131–4. [PubMed: 9364515]

Engel J Jr, Bragin A, Staba R, Mody I. High-frequency oscillations: what is normal and what is not? Epilepsia. 2009; 50:598–604. [PubMed: 19055491]

Fisher RS, Webber WR, Lesser RP, Arroyo S, Uematsu S. High-frequency EEG activity at the start of seizures. J Clin Neurophysiol. 1992; 9:441–8. [PubMed: 1517412]

Gotman J, Levtova V, Farine B. Graphic representation of the EEG during epileptic seizures. Electroencephalogr Clin Neurophysiol. 1993; 87:206–14. [PubMed: 7691551]

Jacobs J, Levan P, Chander R, Hall J, Dubeau F, Gotman J. Interictal high-frequency oscillations (80–500 Hz) are an indicator of seizure onset areas independent of spikes in the human epileptic brain. Epilepsia. 2008; 49:1893–907. [PubMed: 18479382]

Jacobs J, Levan P, Chatillon CE, Olivier A, Dubeau F, Gotman J. High frequency oscillations in intracranial EEGs mark epileptogenicity rather than lesion type. Brain. 2009a; 132:1022–37. [PubMed: 19297507]

Jacobs J, Zelmann R, Jirsch J, Chander R, Dubeau CE, Gotman J. High frequency oscillations (80–500 Hz) in the preictal period in patients with focal seizures. Epilepsia. 2009 Epub.

Jacobs J, Zijlmans M, Zelmann R, Chatillon CE, Hall J, Olivier A, et al. High-frequency electroencephalographic oscillations correlate with outcome of epilepsy surgery. Ann Neurol. 2010; 67:209–20. [PubMed: 20225281]

Jirsch JD, Urrestarazu E, LeVan P, Olivier A, Dubeau F, Gotman J. High-frequency oscillations during human focal seizures. Brain. 2006; 129:1593–608. [PubMed: 16632553]

Khosravani H, Mehrotra N, Rigby M, Hader WJ, Pinnegar CR, Pillay N, et al. Spatial localization and time-dependant changes of electrographic high frequency oscillations in human temporal lobe epilepsy. Epilepsia. 2009; 50:605–16. [PubMed: 18717704]

Lee SA, Spencer DD, Spencer SS. Intracranial EEG seizure-onset patterns in neocortical epilepsy. Epilepsia. 2000; 41:297–307. [PubMed: 10714401]

Mormann F, Andrzejak RG, Elger CE, Lehnertz K. Seizure prediction: the long and winding road. Brain. 2007; 130:314–33. [PubMed: 17008335]

Ogren JA, Wilson CL, Bragin A, Lin JJ, Salamon N, Dutton RA, et al. Three-dimensional surface maps link local atrophy and fast ripples in human epileptic hippocampus. Ann Neurol. 2009; 66:783–91. [PubMed: 20035513]

Otsubo H, Ochi A, Imai K, Akiyama T, Fujimoto A, Go C, et al. High-frequency oscillations of ictal muscle activity and epileptogenic discharges on intracranial EEG in a temporal lobe epilepsy patient. Clin Neurophysiol. 2008; 119:862–8. [PubMed: 18289931]

Schevon CA, Trevelyan AJ, Schroeder CE, Goodman RR, McKhann G Jr, Emerson RG. Spatial characterization of interictal high frequency oscillations in epileptic neocortex. Brain. 2009; 132:3047–59. [PubMed: 19745024]

Spencer SS, Guimaraes P, Katz A, Kim J, Spencer D. Morphological patterns of seizures recorded intracranially. Epilepsia. 1992; 33:537–45. [PubMed: 1592034]

Staba RJ, Wilson CL, Bragin A, Fried I, Engel J Jr. Quantitative analysis of high-frequency oscillations (80–500 Hz) recorded in human epileptic hippocampus and entorhinal cortex. J Neurophysiol. 2002; 88:1743–52. [PubMed: 12364503]

Urrestarazu E, Chander R, Dubeau F, Gotman J. Interictal high-frequency oscillations (100–500 Hz) in the intracerebral EEG of epileptic patients. Brain. 2007; 130:2354–66. [PubMed: 17626037]

Urrestarazu E, Jirsch JD, LeVan P, Hall J, Avoli M, Dubeau F, et al. High-frequency intracerebral EEG activity (100–500 Hz) following interictal spikes. Epilepsia. 2006; 47:1465–76. [PubMed: 16981862]

Worrell GA, Gardner AB, Stead SM, Hu S, Goerss S, Cascino GJ, et al. High-frequency oscillations in human temporal lobe: simultaneous microwire and clinical macroelectrode recordings. Brain. 2008; 131:928–37. [PubMed: 18263625]

Zelmann R, Zijlmans M, Jacobs J, Chatillon CE, Gotman J. Improving the identification of High Frequency Oscillations. Clin Neurophysiol. 2009; 120:1457–64. [PubMed: 19576848]

Zijlmans M, Jacobs J, Zelmann R, Dubeau F, Gotman J. High-frequency oscillations mirror disease activity in patients with epilepsy. Neurology. 2009; 72:979–86. [PubMed: 19289737]

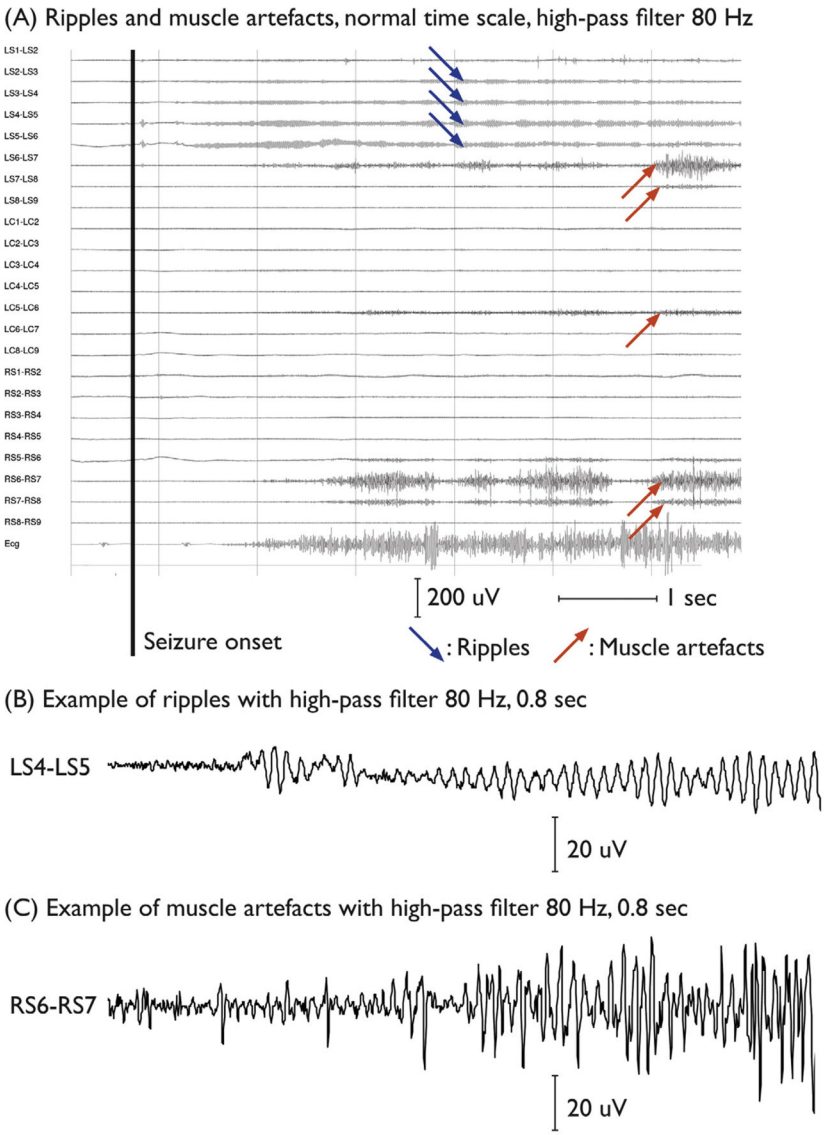

Fig. 1.

Channels with potential muscle artefacts were excluded from the analysis. This was done by reviewing the SEEG at normal time scale with a filter of 80 Hz together with the available epidural, ECG and EMG channels. Muscle artifact can be recognized as a simultaneous high frequency artifact over channels that are potentially outside of the brain, like channels LS6-7 and above, LC5-6 and above and RS5-6 and above in this example. Another clue could be obtained by filtering at lower frequencies as well. If still in doubt, the signal was reviewed at a timescale showing all samples. Muscle artifact shows a less sinusoid shape than HFOs and the frequency spectrum shows relatively more frequencies (Otsubo et al., 2008). Whenever there was doubt, the channel was excluded.

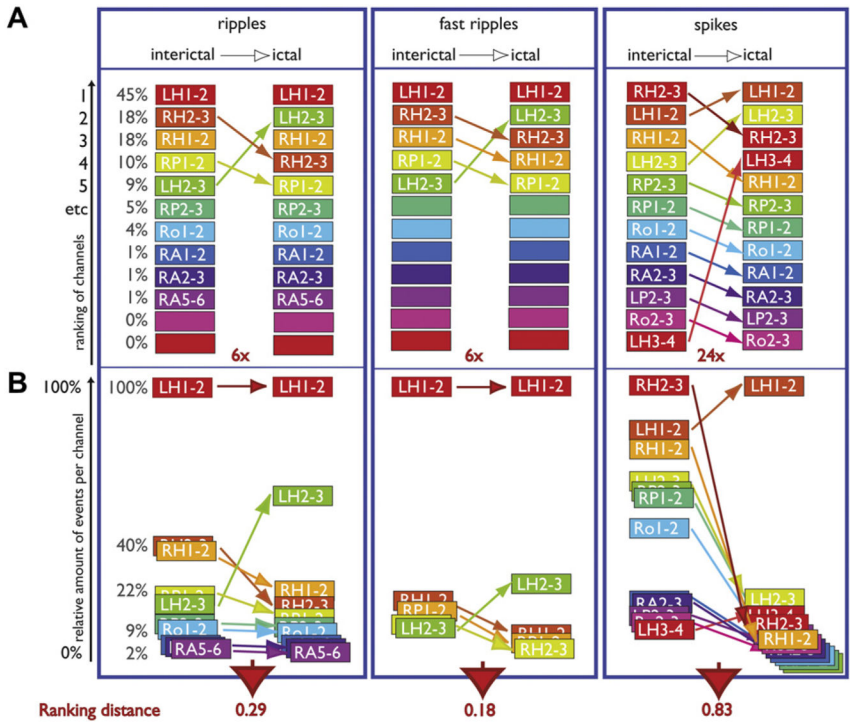

Fig. 2.

Example of calculating the ranking distance between interictal and ictal periods in one patient for ripples, FRs and spikes. A: channels are ranked according to the percentage of time occupied by the events (color is used here to facilitate channel identification; it does not represent percentage of time). Then, arrows indicate the channels for which rankings are different between the two periods, in this case interictal and ictal, and these differences are summed (6×, 6×, 24×). B: same concept as in A except that channels are weighted by their percentage of time occupied and arrows are weighted by their point of origin to allow large changes to influence the outcome more than small changes. So, an equal change in ranking can lead to a greater ranking distance if the relative differences of the changes are higher (in this example ripples compared to FRs: both have six changes in ranking, but the weighted ranking distances are, respectively 0.29 and 0.18). LH1-2, RH1-2, RH2-3 etc. are channel names (Table 1).

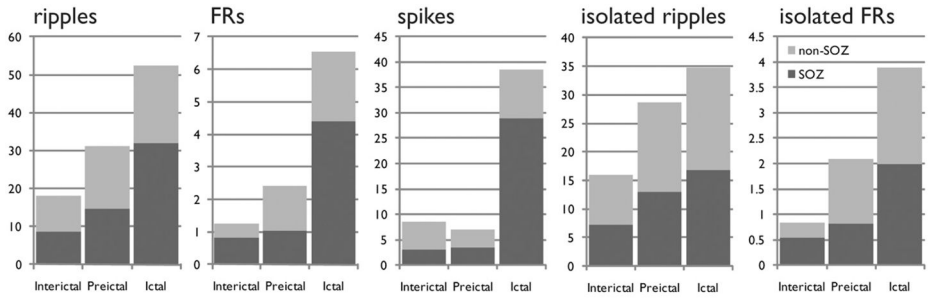

Fig. 3.

Sum of percentages of time (over all channels) occupied by ripples, FRs, spikes, ripples without spikes (R_isol) and FRs without spikes (FR_isol), during the interictal, pre-ictal and ictal periods. The darker grey represents the sum of events in the SOZ-channels (in total 119 channels), while the lighter grey represents the sum of events in the channels outside the SOZ (in total 683 channels). For HFOs there is a significant increase from interictal to pre-ictal and from pre-ictal to ictal, but spikes show a significant decrease pre-ictally. The pre-ictal to ictal increase is greatest for the spikes and relatively low for the HFOs without spikes, especially outside the SOZ.

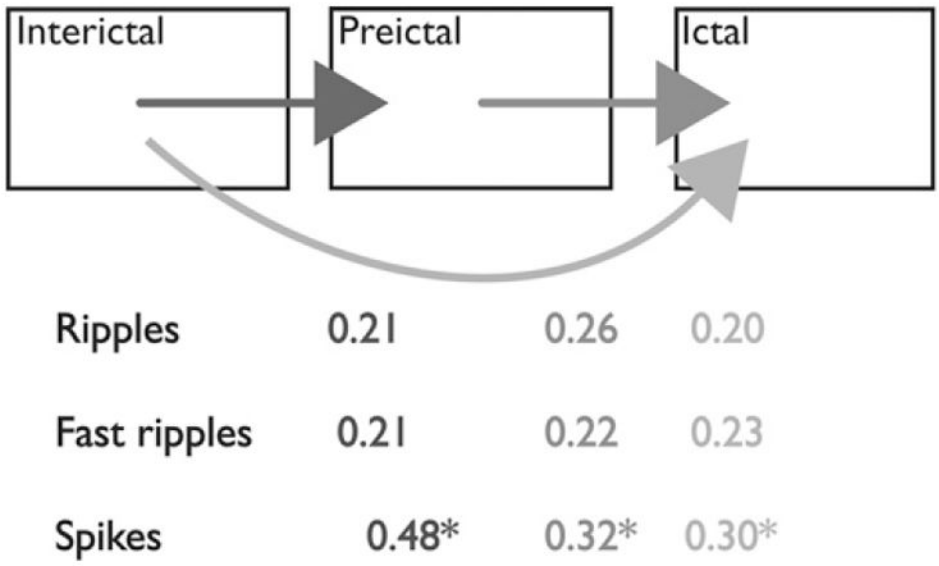

Fig. 4.

mean RKD between rankings of channels for the percentage of time occupied by events between interictal and ictal, interictal and pre-ictal, pre-ictal and ictal. A *means that the value is significantly greater than 0.2 with z-test ($p < 0.05$).

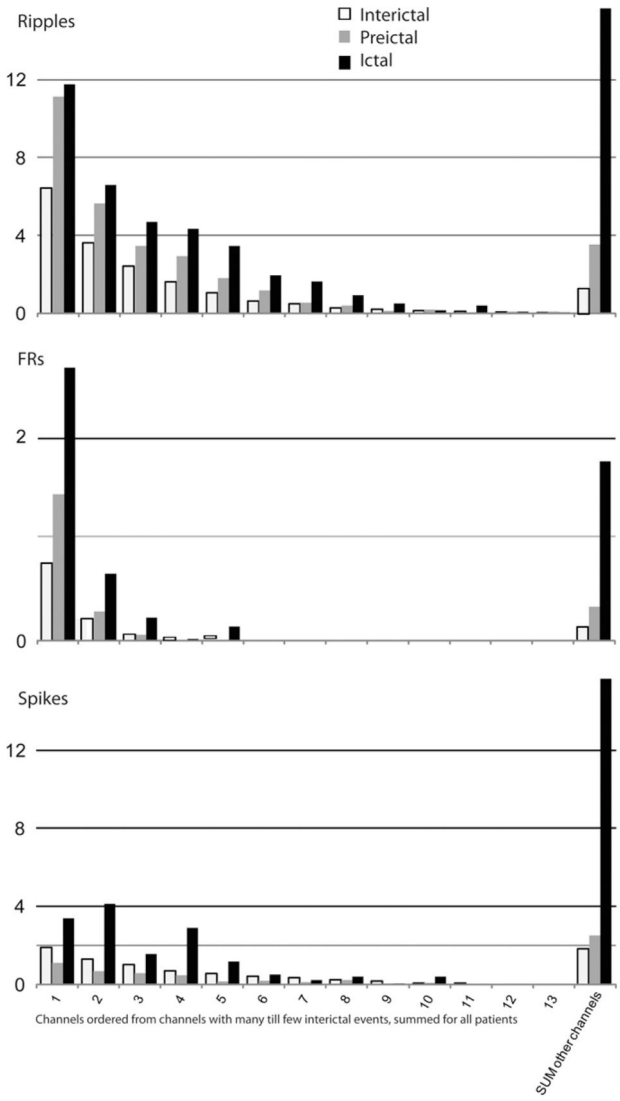

Fig. 5.

Bar graphs of interictal, pre-ictal and ictal amounts (percentage of time) of ripples, FRs and spikes, summed for all 25 patients after separating the channels into groups of “channels with interictal events”, “channels without interictal but with ictal events” (rates below 0.2) and “patients with only ictal events” (not shown). The “channels with interictal events” were ranked for each patient from highest to lowest and the summed up for the interictal as well as the pre-ictal and ictal events. Example: on one patient, channels A and B show interictal spikes with the highest percentage of occupancy in channel A; in a second patient, channels D, C and E show interictal spikes in descending order (and no spikes in channels A and B), the graph would sum up the percentages of channels A and D (rank 1), channels B and C (rank 2) and 0 and E (rank 3). The last bar shows the summation of the “channels with only ictal events”. This bar does also contain interictal events because rates were below 0.2, so not 0. The first light grey bars represents the interictal, the second darker bars the pre-ictal and the last black bars the ictal period. The distribution of spikes over channels differs more

between the ictal and interictal period than the distribution of HFOs: the channels that show most HFOs interictally also show most HFOs ictally; rankings are parallel, unlike for spikes.

Table 1

Number of channels analyzed out of the total number of bipolar channels recorded, and description of the sites of electrode insertion.

Patient	Channels analyzed/recorded	Places of electrodes
1	36/58	LA, LH, LPH, LE, RA, RH, RPH, RE
2	41/52	LC, LOF, LFpl, LFsa, LE, RC, ROF, RE
3	30/53	LT1, LT2, LSMAa, LSMAp, LCa, LCp, LE
4	25/32	RA, RH, RSMA, RC
5	31/44	RA, RH, RPH, ROF, RC, RE
6	41/56	LTP, LA, LH, LPH, RTP, RA, RH, RPH
7	26/56	LSMAa, LSMAp, LFal, LC, RSMAa, RSMAp, RFal
8	30/43	LOF, LTP, LA, LH, LPH, LE
9	30/57	LT1, LA, LOP, LOF, LCa, LCP, LOC
10	40/53	LA, LH, RA, RH, RPH, RAG, RE
11	6/13	LPH, LE
12	28/32	RA, RH, ROCs, ROCi
13	24/38	LA, LH, LE, RA, RH, RE
14	38/48	RA, RH, ROF, ROFm, RCa, RSMA
15	34/43	LTP, LA, LH, LPH, LOF, LE
16	26/43	RSMA, RC, RIPM, RIPS, RSPS, RE
17	27/35	LT1, LPH, LAG, LOC, LE
18	57/64	LA, LH, RA, RH, LOF, LCa, ROF, RCa
19	42/58	LA, LH, LPH, LE, RA, RH, RPH, RE
20	19/37	LCPas, LCPps, LCPai, LCPpi, LE
21	27/38	RA, RH, RPH, RIS
22	43/48	LA, LH, LPH, RA, RH, RPH
23	24/42	RA, RH, RPH, RHE, RE
24	45/56	LCa, LCp, LOF, RCa, RCp, ROF, RFa
25	32/44	RA, RH, RPH, RAN, RPN, RE

R: right; L: left; temp: temporal; F: frontal; C: central; A: amygdala; H: hippocampus; PH: parahippocampus; E: epidural, Ca/p: cingulate (anterior/posterior); OF: orbitofrontal; Fpl: frontal (posterior lateral); Fsa: frontal (superior anterior); OFm: orbitofrontal (mesial), T1: temporal 1st gyrus; T2: temporal 2nd gyrus; SMAa/p: supplementary motor area (anterior/posterior); TP: temporal pole; Fal: frontal (anterior lateral); OP: operculum; CP: centroparietal; AG: angular gyrus; OCs/i: occipital (superior/inferior); IPM: inferior primary motor cortex; IPS: inferior sensory cortex; SPS: superior primary sensory; IS: isthmus; HE: Heschl gyrus; AN: anterior from nodule; PN: posterior from nodule.

Table 2

Averaged ratios of all patients between the average percentage of time with events in the SOZ compared to the non-SOZ, in brackets is the number of patients out of 25 with a positive ratio. A positive ratio means that the average percentage in the SOZ is higher than in the non-SOZ. What can be seen is that all events have a higher ratio in the ictal period and that ripples show higher ratios. The difference between interictal and ictal is greater for spikes than for ripples and FRs, meaning that the HFOs seem more stable over different states than spikes. The lower number for FRs in the pre-ictal epoch probably results from low rates of FRs in this short epoch.

	Ripples	FR	Spikes
Interictal	0.45 (20)	0.33 (17)	0.28 (13)
Pre-ictal	0.46 (19)	0.10 (11)	0.35 (18)
Ictal	0.63 (22)	0.48 (18)	0.58 (21)