Opinion Paper

High frequency oscillations as markers of epileptogenic tissue – End of the party?

Tommaso Fedele [a,*], Georgia Ramantani [b], Johannes Sarnthein [c,d]

[a] Institute of Cognitive Neuroscience, Higher School of Economics – National Research University, Moscow, Russian Federation
[b] Neuropediatrics, University Children's Hospital Zurich, Switzerland
[c] Neurosurgery, University Hospital Zurich, Switzerland
[d] Neuroscience Center Zurich, University of Zurich, Switzerland

1. Introduction

Over 20 years of enthusiastic research have served to establish high frequency oscillations (HFO) as a promising biomarker of epileptogenicity, both in animal models and in refractory focal epilepsy patients (Jacobs et al., 2010, 2012; Fedele et al., 2017b; Frauscher et al., 2017; Zijlmans et al., 2017; Gotman, 2018). Several studies have relied on higher interictal HFO occurrence rates to identify the seizure onset zone (SOZ), and thus to detect the epileptogenic tissue in patients undergoing presurgical workup or epilepsy surgery (Jacobs et al., 2010, 2012; Frauscher et al., 2017; Zijlmans et al., 2017). Latest reports showed that residual HFO after epilepsy surgery have the potential to predict poor seizure outcome in the individual patient (van't Klooster et al., 2015), emphasizing the key role of post-resection ECoG for optimal seizure control (van't Klooster et al., 2017). Classifying brain regions as "SOZ" and "non-SOZ" in a series of refractory focal epilepsy cohorts was guided by the notion that HFO generally present a strong correlation with epileptogenicity and are thus more frequently encountered in the SOZ. HFO rates in these studies were found to depend on several factors, e.g., antiepileptic drug combinations and their withdrawal during presurgical workup (Zijlmans et al., 2009), sleep homeostasis (von Ellenrieder et al., 2017), or localization in different regions throughout the brain (Guragain et al., 2018). Nevertheless, taken together, these studies provided converging evidence of the strong association of HFO with the epileptogenic zone (EZ) and paved the way towards the potential use of HFO, in a prospective way, to guide surgery planning in the individual patient (Fedele et al., 2017b).

However, recent reports (Gliske et al., 2018; Jacobs et al., 2018; Roehri et al., 2018) have raised serious doubts about the clinical utility of localization diagnosis deriving from HFO. Is the party over? Mindful of twenty years of enthusiastic and prospering research on HFO and before declaring the party over, cleaning up, and going home, we would like to take some time for some more thoughts. We will have three long sighs pondering on three key issues, namely:

– How to validate HFO?
– How to define clinically relevant HFO?
– How to select data for HFO detection?

2. HFO as a biomarker should be validated against seizure outcome

Biomarkers and their added value should be generally tested in an appropriate clinical setting to ensure their utility and reliability. In the case of epilepsy surgery for refractory focal epilepsy, the location of the SOZ, though important, does not necessarily determine the extent of the EZ (Asano et al., 2013; Vakharia et al., 2018). Thus, evaluating the clinical utility of HFO against the SOZ alone is clearly not reasonable. The main purpose of a biomarker for epileptogenic tissue is to delineate the EZ, which is defined as the brain area whose resection leads to seizure freedom. Although we cannot directly define the EZ, we can assume that the EZ was included in the resection in patients that achieved seizure freedom and was not completely resected in patients with seizure recurrence. Therefore, HFO as a biomarker for epileptogenicity should be rather validated against postsurgical seizure freedom, i.e. whether the individual patient became seizure free following the resection of HFO-generating cortical areas or not. Unfortunately, this level of validation is rarely performed because linking HFO rate in the resected tissue to postsurgical seizure outcome demands a long breath, often longer than the time limits of financial support, grant reports, and individual career steps. Nevertheless, the association of the resected brain region to postsurgical seizure outcome at ≥1 year follow up is clearly the most appropriate measure for the reliable validation of clinically relevant HFO (Fedele et al., 2017b; van't Klooster et al., 2017; Gliske et al., 2018; Jacobs et al., 2018).

3. Clinically relevant HFO should be defined prospectively

At the beginning of the HFO research era, PhD students and young aspiring neurologists were assigned the meticulous and

---

* Corresponding author.
E-mail address: tofedele@hse.ru (T. Fedele).

time-consuming chore of visual identification and annotation of HFO in multichannel 2 kHz invasive EEG traces (Jacobs et al., 2010). Based on these original datasets that contained visually marked and interobserver-validated HFO, automatic detection algorithms were later developed (Zelmann et al., 2012). HFO consist of extremely variable patterns in space and time that are mathematically modeled through optimized spectral filters, whitening, entropy-based approaches, neural networks, etc. Nowadays, several software packages for automatic HFO detection are readily accessible that perform fast, are free of human bias, and provide reproducible results (Zijlmans et al., 2017). However, the datasets used to train HFO detectors have only rarely been made openly accessible (Fedele et al., 2017a; Guragain et al., 2018), although their comparative analysis could prove crucial to improve detection algorithms and benchmark them against each other. Furthermore, these detection algorithms have only rarely been validated against postsurgical seizure freedom (van't Klooster et al., 2015, 2017; Fedele et al., 2016, 2017b). In order to establish the clinical utility of HFO as a biomarker for epileptic tissue and move a big step forward in the development of sophisticated algorithms for HFO detection, we need to define HFO whose removal predicts seizure freedom and train the algorithms – with joint forces across different software packages – towards their detection. This process is crucial, complex and yet feasible, as has been shown in recent studies from our group (Fedele et al., 2016, 2017b). The automated identification of clinically relevant HFO in the context of epilepsy surgery is the prerequisite for their ultimate validation and wide utilization as a biomarker.

4. Sufficient data should be selected for HFO detection

Server capacity in epilepsy centers nowadays allows to store 2 kHz/100 channel data over entire nights for several patients. But should all this data actually be utilized for HFO analysis or would carefully selected excerpts suffice for clinically meaningful results? HFO localization diagnostics requires spatial profiles that remain stable over time, accurately reflecting the network properties without the need to wait for seizures. The data quality and representativity will determine the validity of results.

To provide reproducibility, we need to test-retest HFO with reasonably homogenous physiological properties over several time epochs. One main source of HFO variability stems from their occurrence according to the schedule of sleep homeostasis (von Ellenrieder et al., 2017). During slow wave sleep (SWS), HFO show the highest spatial specificity (Bagshaw et al., 2009). While sleep stage assessment relies on scalp EEG and submental myography, the identification of SWS directly from invasive EEG remains challenging. To establish reliability, we propose to test-retest the spatial profile of HFO rates across several SWS epochs from each patient during a single night or, preferably, across several nights (Fedele et al., 2017b). In a previous study from our group, we confirmed a high reliability of HFO for seizure outcome prediction (85%) only if the test-retest analysis showed a stable spatial profile of HFO over time. This approach has been recently applied to a larger cohort (Gliske et al., 2018). However, in that study, the data available for analysis stemmed from a fixed interval during the night (1–3 am), irrespective of the sleep stage. In our opinion, none of the cases in the study challenge the significance of HFO as reliable predictors of postsurgical seizure outcomes. The authors present complex patients with multiple SOZ varying over the recording period. In that scenario, the variability of HFO rates may actually reflect the multifocal nature of the epilepsy, thus rather supporting than challenging the value of HFO as biomarker of epileptogenicity.

While HFO analysis aims for improved localization, beyond the analysis of conventional biomarkers of epileptogenicity, there are several factors that affect both approaches alike, among them patient selection and spatial sampling of the recording sites. Patient selection is important and must be well documented since HFO may have a particularly high added value in some patient groups, for example among the pediatric population. Spatial sampling is an important factor, since a sparse invasive EEG implantation may miss critical locations. Here, test-retest analysis may provide an antidote. Insufficient coverage of the EZ by the implanted electrodes prohibits access to critical information on the seizure generator, and this is often mirrored by the highly variable HFO detection (Fedele et al., 2017b, Gliske et al., 2018). In this case, too, a consistent test-retest analysis may confirm the high reliability of HFO for seizure outcome prediction in the individual patient.

In conclusion, good practice in HFO detection should comprise the use of a detector validated against seizure outcome, the analysis of several SWS epochs, and the performance of test-retest analysis to ensure the stability of the spatial profile. Once these requirements are met, in our opinion there may well be a role for HFO in tailoring the treatment of refractory focal epilepsy patients and thus improving their outcomes.

So, now get up, there is still more research to be done on HFO!

Conflict of interest

The authors have no potential conflicts of interest to disclose.

Funding

References

Asano E, Brown EC, Juhasz C. How to establish causality in epilepsy surgery. Brain Dev 2013;35:706–20.
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.
Fedele T, Burnos S, Boran E, Krayenbühl N, Hilfiker P, Grunwald T, et al. Dataset: resection of high frequency oscillations predicts seizure outcome in the individual patient. CRCNS. Berkeley: CRCNS; 2017a. https://crcns.org/data-sets/methods/ieeg-1/about-ieeg-1.
Fedele T, Burnos S, Boran E, Krayenbühl N, Hilfiker P, Grunwald T, et al. Resection of high frequency oscillations predicts seizure outcome in the individual patient. Scientific Reports 2017b;7:13836.
Fedele T, van't Klooster M, Burnos S, Zweiphenning W, van Klink N, Leijten F, et al. Automatic detection of high frequency oscillations during epilepsy surgery predicts seizure outcome. Clin Neurophysiol 2016;127:3066–74.
Frauscher B, Bartolomei F, Kobayashi K, Cimbalnik J, van't Klooster MA, Rampp S, et al. High-frequency oscillations: the state of clinical research. Epilepsia 2017;58:1316–29.
Gliske SV, Irwin ZT, Chestek C, Hegeman GL, Brinkmann B, Sagher O, et al. Variability in the location of high frequency oscillations during prolonged intracranial EEG recordings. Nat Commun 2018;9:2155.
Gotman J. Oh surprise! Fast ripples on scalp EEG. Clin Neurophysiol 2018;129:1449–50.
Guragain H, Cimbalnik J, Stead M, Groppe DM, Berry BM, Kremen V, et al. Spatial variation in high-frequency oscillation rates and amplitudes in intracranial EEG. Neurology 2018;90:e639–46.
Jacobs J, Staba R, Asano E, Otsubo H, Wu JY, Zijlmans M, et al. High-frequency oscillations (HFOs) in clinical epilepsy. Progr Neurobiol 2012;98:302–15.
Jacobs J, Wu JY, Perucca P, Zelmann R, Mader M, Dubeau F, et al. Removing high-frequency oscillations: a prospective multicenter study on seizure outcome. Neurology 2018;91:e1040–52.
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.

Roehri N, Pizzo F, Lagarde S, Lambert I, Nica A, McGonigal A, et al. High-frequency oscillations are not better biomarkers of epileptogenic tissues than spikes. Ann Neurol 2018;83:84–97.

Vakharia VN, Duncan JS, Witt J-A, Elger CE, Staba R, Engel Jr J. Getting the best outcomes from epilepsy surgery. Ann Neurol 2018;83:676–90.

van't Klooster MA, van Klink NE, Leijten FS, Zelmann R, Gebbink TA, Gosselaar PH, et al. Residual fast ripples in the intraoperative corticogram predict epilepsy surgery outcome. Neurology 2015;85:120–8.

van't Klooster MA, van Klink NEC, Zweiphenning W, Leijten FSS, Zelmann R, Ferrier CH, et al. Tailoring epilepsy surgery with fast ripples in the intraoperative electrocorticogram. Ann Neurol 2017;81:664–76.

von Ellenrieder N, Dubeau F, Gotman J, Frauscher B. Physiological and pathological high-frequency oscillations have distinct sleep-homeostatic properties. Neuroimage Clin 2017;14:566–73.

Zelmann R, Mari F, Jacobs J, Zijlmans M, Dubeau F, Gotman J. A comparison between detectors of high frequency oscillations. Clin Neurophysiol 2012;123:106–16.

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.

Zijlmans M, Worrell GA, Dumpelmann M, Stieglitz T, Barborica A, Heers M, et al. How to record high-frequency oscillations in epilepsy: a practical guideline. Epilepsia 2017;58:1305–15.