



Are HFOs Still UFOs? The Known and Unknown About High Frequency Oscillations in Epilepsy Surgery

High-Frequency Oscillations, Extent of Surgical Resection, and Surgical Outcome in Drug-Resistant Focal Epilepsy.

Haegelen C, Perucca P, Chatillon CE, Andrade-Valenca L, Zelmann R, Jacobs J, Collins DL, Dubeau F, Olivier A, Gotman J. *Epilepsia* 2013;54:848–857.

PURPOSE: Removal of areas generating high-frequency oscillations (HFOs) recorded from the intracerebral electroencephalography (iEEG) of patients with medically intractable epilepsy has been found to be correlated with improved surgical outcome. However, whether differences exist according to the type of epilepsy is largely unknown. We performed a comparative assessment of the impact of removing HFO-generating tissue on surgical outcome between temporal lobe epilepsy (TLE) and extratemporal lobe epilepsy (ETLE). We also assessed the relationship between the extent of surgical resection and surgical outcome. **METHODS:** We studied 30 patients with drug-resistant focal epilepsy, 21 with TLE and 9 with ETLE. Two-thirds of the patients were included in a previous report and for these, clinical and imaging data were updated and follow-up was extended. All patients underwent iEEG investigations (500 Hz high-pass filter and 2,000 Hz sampling rate), surgical resection, and postoperative magnetic resonance imaging (MRI). HFOs (ripples, 80–250 Hz; fast ripples, > 250 Hz) were identified visually on a 5–10 min interictal iEEG sample. HFO rates inside versus outside the seizure-onset zone (SOZ), in resected versus nonresected tissue, and their association with surgical outcome (ILAE classification) were assessed in the entire cohort, and in the TLE and ETLE subgroups. We also tested the correlation of resected brain hippocampal and amygdala volumes (as measured on postoperative MRIs) with surgical outcome. **KEY FINDINGS:** HFO rates were significantly higher inside the SOZ than outside in the entire cohort and TLE subgroup, but not in the ETLE subgroup. In all groups, HFO rates did not differ significantly between resected and nonresected tissue. Surgical outcome was better when higher HFO rates were included in the surgical resection in the entire cohort and TLE subgroup, but not in the ETLE subgroup. Resected brain hippocampal and amygdala volumes were not correlated with surgical outcome. **SIGNIFICANCE:** In TLE, removal of HFO-generating areas may lead to improved surgical outcome. Less consistent findings emerge from ETLE, but these may be related to sample size limitations of this study. Size of resection, a factor that was ignored and that could have affected results of earlier studies did not influence results.

Ripple Classification Helps to Localize the Seizure-Onset Zone in Neocortical Epilepsy.

Wang S, Wang IZ, Bulacio JC, Mosher JC, Gonzalez-Martinez J, Alexopoulos AV, Najm IM, So NK. *Epilepsia* 2013;54:370–376.

PURPOSE: Fast ripples are reported to be highly localizing to the epileptogenic or seizure-onset zone (SOZ) but may not be readily found in neocortical epilepsy, whereas ripples are insufficiently localizing. Herein we classified interictal neocortical ripples by associated characteristics to identify a subtype that may help to localize the SOZ in neocortical epilepsy. We hypothesize that ripples associated with an interictal epileptiform discharge (IED) are more pathologic, since the IED is not a normal physiologic event. **METHODS:** We studied 35 patients with epilepsy with neocortical epilepsy who underwent invasive electroencephalography (EEG) evaluation by stereotactic EEG (SEEG) or subdural grid electrodes. Interictal fast ripples and ripples were visually marked during slow-wave sleep lasting 10–30 min. Neocortical ripples were classified as type I when superimposed on epileptiform discharges such as paroxysmal fast, spike, or sharp wave, and as type II when independent of epileptiform discharges. **KEY FINDINGS:** In 21 patients with a defined SOZ, neocortical fast ripples were detected in the SOZ of only four patients. Type I ripples were detected in 14 cases almost exclusively in the SOZ or primary propagation area (PP) and marked the SOZ with higher specificity than interictal spikes. In contrast, type II ripples were not correlated with the SOZ. In 14 patients with two or more presumed SOZs or nonlocalizable onset pattern, type I but not type II ripples also occurred in the SOZs. We found the areas with only type II ripples outside of the SOZ (type II-O ripples) in SEEG that localized to the primary motor cortex and primary



visual cortex. SIGNIFICANCE: Neocortical fast ripples and type I ripples are specific markers of the SOZ, whereas type II ripples are not. Type I ripples are found more readily than fast ripples in human neocortical epilepsy. Type II ripples may represent spontaneous physiologic ripples in the human neocortex.

Commentary

Both of the above-cited studies examine high frequency oscillations in intracranial EEG and their relationship to the seizure onset zone or outcome after epilepsy surgery. Haegelen et al. find higher rates of HFO of any frequency in the seizure onset zone in temporal lobe epilepsy but not in extratemporal epilepsy. Patients had better outcomes if areas with a higher HFO rate were included in the resected tissue. However, these findings were not replicated for extratemporal lobe epilepsy, which could be just be a result of the small sample size of extratemporal patients in their study ($n = 9$). Wang et al. try to close this gap and examined HFOs in neocortical epilepsy in 39 patients. They found that fast ripples and what they called “type I ripples” correlated with the seizure onset zone. The ultimate goal of both studies was to find a biomarker for the seizure onset zone to guide epilepsy surgery.

It seems generally acknowledged that high frequency oscillations includes any oscillations above 80 Hz, while oscillations between 30–80Hz are frequently referred to as “fast gamma activity.” Frequencies and definitions of HFOs vary significantly in the literature and it is mandatory to define the frequency band of the respective oscillation (1). HFOs are often divided into ripples and fast ripples. Ripples seem to be generally accepted as oscillations between 80–250 Hz and fast ripples as oscillations above 250 Hz. In Wang et al., fast ripples occurred rarely in neocortical epilepsy, as only 4 of the 39 patients with neocortical epilepsy were found to have oscillations above 250. But if fast ripples occurred, they seemed to correlate with the seizure onset zone as previously shown in hippocampal epilepsy (2). Haegelen et al. could not uniformly confirm the clear relationship between fast ripples and the SOZ. In their entire cohort, there was no correlation, but in the temporal lobe subpopulation there was—maybe again a problem of sample size. Slower oscillations (ripples) however correlated with the SOZ in the entire cohort.

The relationship of HFOs to epileptic spikes still remains to be fully elucidated. Wang et al. try to address this problem by defining Type I and Type II ripples. Type I occur simultaneous with spikes, Type II independent of spikes (3). Only HFOs associated with spikes indicated the seizure onset zone. The problem of possible artifact just by merely high pass filtering interictal spikes remains, as this may produce artifactual waveforms that appear as ripples. Both studies address this problem with the number of oscillations that are considered a ripple or HFO. Three undulations do not count as HFO, but four do. This distinction seems somewhat arbitrary, but certainly may help to operationally describe the phenomenon,

Both studies examine HFOs during slow-wave sleep; during clearly interictal periods. Interictal neurophysiology

to describe seizure onset zones in the past has been disappointing. HFOs peri-ictally could be of greater significance as a biomarker for the seizure onset zone (4). It certainly could be explored as another early detection tool of an impending seizure (4).

Wang et al. claim that the spatial distribution of HFOs is more precise than interictal epileptiform activity such as spikes. However, the number of observed HFOs in the seizure onset zone is merely relatively increased in number in comparison to the HFO activity seen in non-seizure onset zones. Since it can be difficult to measure relatively increased abnormalities, it remains difficult to implement interpretation of HFOs as a clinically useful tool.

Another barrier for implementing HFO counts as a clinically useful tool is certainly the amount of work and time required to identify HFOs. Especially with patients undergoing intracranial studies with subdural grid electrodes, surgical decisions have to be made rather promptly. Attempts of automated detection of HFO could significantly speed up the process and seem to be more feasible as alternative method in the clinical realm as compared to a research tool (3, 5).

Wang et al. address the question whether HFO are a physiological rather than a pathological process and examine HFO in the visual cortex and over the motor areas. They defined another type of HFO, the Type II-O ripple, which occurs over certain functional neocortex, namely the visual and motor cortex. The question remains what distinguishes a physiologic from a pathologic HFO? High frequency oscillations have been described with a variety with cognitive processes, but mainly in frequencies below 100 Hz, in many cases due to recording techniques that do not allow higher frequency band recordings (1). The exact relationship to what epileptologists consider an epilepsy-associated ripple or HFO remains unclear.

Electrode design could influence the occurrence, appearance, and frequency of HFOs. Haegelen et al. assessed only HFO recorded with custom-designed depth electrodes. Wang et al. assessed HFO in subdural grid/standard depth electrodes and stereo-EEG electrodes of smaller diameter. Although HFOs can be recorded with various electrode designs, there are subtle differences (6). Microelectrodes may be even more precise in recording faster frequencies and more exact in assessing neuronal assemblies (7). Speaking about neuronal assemblies, in *in vitro* models epileptogenic high frequency oscillations have been associated with synchronized firing of interneurons, which are regulated by long projections in the septo-hippocampal formation (8).

The Haegelen et al. study demonstrates another important point: Surgical outcome studies can be heavily confounded by volume of resection. They distinctly tried to eliminate this con-



founder. Their elaborate method to calculate surgical resection volume clearly demonstrates how difficult this can be. Exact surgical volumes cannot be easily obtained postoperatively. It is also interesting that they did not find a correlation between volume of resection and outcome.

In conclusion, HFOs are oscillations that we observe, but we are still not entirely sure of their clinical significance and how they could help epileptologists plan for epilepsy surgery. They have some relationship to the epileptic process, but we are still unclear about the details. In that regard, HFOs are very similar to UFOs: We observe a phenomenon, but we do not know what they mean or where they come from. A great opportunity for further exploration!

by Barbara C. Jobst, MD

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