# Trends in the use of automated algorithms for the detection of high frequency oscillations associated with human epilepsy

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## Summary

High frequency oscillations (HFOs) in intracranial EEG are a promising biomarker of the epileptogenic zone and tool for surgical planning. Many studies have shown that a high rate of HFOs (number per minute) is correlated to the seizure onset zone, and complete removal of HFO-generating brain regions has been associated with seizure free outcome after surgery. In order to use HFOs as a biomarker, these transient events must first be detected in electrophysiological data. Because visual detection of HFOs is time consuming and suffers from low interrater reliability, many automated algorithms have been developed, and they are increasingly being used for such studies. However, there is very little guidance on how to select an algorithm, implement it in a clinical setting, and validate the performance. Therefore, we aim to review automated HFO detection algorithms, focusing on conceptual similarities and

differences between them. We summarize the standard steps for data pre-processing, as well as post-processing strategies for rejection of false positive detections. We also detail four methods for algorithm testing and validation, and we describe the specific goal achieved by each one. We briefly review direct comparisons of automated algorithms applied to the same dataset, emphasizing the importance of optimizing detection parameters. Then, to assess trends in the use of automated algorithms and their potential for use in clinical studies, we review evidence for the relationship between automatically detected HFOs and surgical outcome. We conclude with practical recommendations and propose standards for the selection, implementation, and validation of automated HFO detection algorithms.

## Key words

Ripple, fast ripple, seizure localization, biomarker, seizure onset zone, epileptogenic zone

## Key points

- This article reviews automated HFO detection algorithms and their implementation in clinical studies comparing HFOs to surgical outcome
- Initial detection of HFOs relies on a wide variety of energy-based methods, whose detection results will be highly overlapping
- It is crucial to optimize detection parameters, remove artifacts from the data, and reject false positive detections
- Automatic detection has been used to identify significant correlations between removal of HFO-generating regions and surgical outcome
- Implementation and optimization of automatic detection should be standardized to facilitate identification of trends across studies

# 1. Introduction

Epilepsy is one of the most common neurological disorders, affecting more than 65 million people worldwide.[1] Roughly one third of patients with epilepsy have poorly controlled seizures despite optimal treatment with medication.[2] In such cases, surgical resection of the epileptogenic zone (EZ) is an alternative and effective treatment.[3, 4] Post-surgical seizure freedom depends on the accurate localization of the EZ, but there are currently no validated biomarkers of the EZ.[5, 6] The present gold standard for epilepsy surgery is removal of the seizure onset zone (SOZ), defined as the brain area where seizure activity is first seen. However, the SOZ is difficult to localize and does not delineate the full extent of the EZ. Thus, in addition to the SOZ, other electrophysiological and non-EEG biomarkers are needed to help localize the EZ.

High frequency oscillations (HFOs) have been studied extensively in the past two decades as a potential biomarker of the EZ.[7] HFOs are transient electrographic events consisting of multiple sinusoid-like waves in the 80 to 500Hz frequency range that clearly stand out from the background (Figure 1).[8] To analyze HFOs, high sampling rate data must be collected, which requires the use of a specialized amplifier.[9] HFOs can be measured with both intracranial EEG and scalp EEG,[8] although frequent artifacts (signals of non-neural origin) and the low power associated with high frequency activity, especially in scalp recordings, make accurate detection a challenge.[9] After the data are recorded, interictal HFOs are detected in the signal from each channel using visual or automatic detection, and the rates (number per minute per channel) are calculated. Numerous studies show that the HFO rate is higher inside than outside the SOZ,[10-16] and there is good evidence that removal of brain regions exhibiting a high rate of HFOs correlates with good surgical outcome.[17-19] These data suggest that regions containing channels with high HFO rates are potential surgical targets.

However, the precise cellular mechanism by which HFOs are generated remains unknown, which has prevented establishment of a consensus on the features (e.g., amplitude, duration, frequency, and number of cycles) used to describe an HFO. Therefore, current studies rely on an empirical definition derived from visual observation.[20, 21] Different research groups choose different definitions, e.g., a criterion of three or more oscillations vs. four or more oscillations in each HFO. Moreover, physiological HFOs in the ripple band, such as those occurring in the

hippocampus,[22] have features that overlap with those of pathological HFOs.[23-25] This makes both visual and automatic detection problematic.

For HFO detection, the earliest studies relied on visual methods using one or more experienced reviewers.[26, 27] However, this is a time-consuming process, especially when analyzing more than a few minutes of data. Also, the inter-reviewer reliability is often inadequate.[28-30] This suggests the need for fast and accurate automatic detection algorithms. There are many published automatic detection algorithms, but almost no recommendations on when one algorithm should be chosen over the others and how to select parameters for implementation. Directly comparing different algorithms is non-trivial because it is rare for multiple algorithms to be applied to the same dataset, and the performance of each algorithm depends on the choice of parameters. Here we provide a comprehensive review of current automated algorithms. First, we compare and contrast the methods, then we identify trends in the use of automated detection in clinical studies for SOZ/EZ localization. Lastly, we suggest standards for the development and implementation of automated detectors.

## 2. Automated detection of HFOs

### 2.1 Data acquisition and preprocessing

Intracranial EEG (iEEG) data for clinical HFO research is commonly recorded using standard macroelectrode contacts on grid and strip electrocorticogram (ECoG) electrodes, depth electrodes, and stereotactic EEG (SEEG). These electrodes have surface areas ranging from roughly 1 to 10mm$^2$.[31] The data are typically re-referenced offline to a bipolar montage, and visual review is used to reject channels containing significant artifacts.[32, 33] For HFO analysis, the acquired iEEG data is bandpass filtered to restrict the range of frequencies, predominantly using finite impulse response filters with forward and reverse filtering to minimize phase distortion.[34] Based on early results, research has primarily focused on two frequency bands: the ripple band (80-250Hz) and the fast ripple band (250-500Hz).[26] Whitening, or spectral equalization, can be done to compensate for the fact that EEG power decreases as frequency increases.[30, 35-37] Data for HFO analysis are normally acquired at 2000Hz or more using specialized amplifiers. However, some studies have used standard clinical sampling rates to

study oscillations in the gamma band, venturing away from the conventional definition of HFOs.[30, 38]

HFOs occur with the highest probability during non-rapid eye movement (NREM) sleep,[14] and muscle artifacts are less frequent during these periods; hence, NREM is most commonly used for detection of HFOs. In studies where scalp EEG is unavailable, NREM sleep is identified via increased power in low frequency bands[39, 40] or additional EOG and EMG electrodes.[17, 41] However, some studies do not sleep stage because scalp EEG is not a standard procedure for long-term intracranial monitoring.[42] HFOs are typically detected in short epochs of data, ranging from 1 to 10 mins, but recent evidence suggests that longer epochs may be necessary.[43]

Although HFOs have been identified in both ictal and interictal EEG, HFO studies predominantly use interictal data, taken a few hours before and after seizures. The use of interictal data negates the need to wait for rare and unpredictable seizures, and it reduces the amount of high sampling rate data that must be recorded and stored. Moreover, data from Zijlmans et al. suggested that HFOs occur in the same brain regions during ictal and interictal periods.[44] Residual anesthesia and anti-seizure medications can suppress HFO activity,[45, 46] so data is typically collected on or after the second night of recording.

## 2.2 Automated algorithms for initial event detection

A critical step in the detection of HFOs is separating them from the background activity. For this initial detection step, existing algorithms use energy-based metrics (Table 1). Among the many energy measures that exist, the most commonly used are root-mean-square (RMS) amplitude,[32, 33, 42, 47-50] power,[51, 52] line length,[11, 30, 51, 53] and Hilbert transform envelope.[54, 55] Other methods include a median filter[56] and amplitude of the local peaks in the filtered data.[40, 57] A multi-channel detection method based on RMS and line length was also proposed to account for simultaneous measurement of multiple adjacent electrodes and eliminate the need for manual channel selection.[58] Several of the energy-based metrics (RMS, power, line length, and median filter) are calculated for short windows of filtered data with or without overlap, which adds an additional parameter. The others (Hilbert envelope, amplitude of local peaks) can be calculated without windowing the data.

After calculating the energy, events that exceed a pre-determined threshold for a minimum duration are identified as potential HFOs. The threshold is typically a number of standard deviations above the mean value or a non-parametric threshold based on the cumulative distribution function, e.g., events with an energy above the 99$^{th}$ percentile. The threshold can be set for the entire duration of the data or for short epochs of data, which accounts for local modulations in the energy of the background activity. These detectors may further require a minimum number of oscillatory cycles for events to qualify as HFOs. Events that are separated by less than a minimum time period are often concatenated to form one single event. The parameters can be adjusted to change the sensitivity of the detector, but a highly sensitive detector may be preferred if it is paired with post-processing steps to reject false positives (see Section 2.3). While there are exceptions, the events detected by these methods will have significant overlap because the different energy metrics are highly correlated (Figure 2). Energy-based methods are easy to relate to visual detection and have a low barrier to implementation, but accurate performance is highly dependent on optimization of the detection parameters.

## 2.3 Post processing and rejection of false positives

Filtering of a sharp transient in the EEG will produce a burst of high frequency activity, which may be falsely detected as an HFO.[34] Signals of non-neural origin, such as muscle activity and harmonics of electrical line noise, can also cause false positive detections.[59] For this reason, many algorithms include steps for rejection of false positives after the initial detection (Table 1). While this increases the specificity of the detector, it also introduces additional parameters that must be optimized. Visual rejection is commonly used, especially coupled with low sensitivity detectors. Automated methods have also been developed, as visual marking is not feasible when the number of detected events is high. These include techniques based on the time domain signal, the time-frequency decomposition, and machine learning:

### *2.3.1 Time domain techniques*

Detected events may be rejected if the duration exceeds a threshold,[56] indicating possible contributions of muscle activity. Special methods for detecting fast DC-shifts in the raw data and artifacts in the common average (indicating that the event is too spatially widespread to be

an HFO) have been proposed.[42] Restricting the number of zero crossings in the raw data has also been used as a means of rejecting false HFOs.[56]

### *2.3.2 Time-Frequency decomposition*

Time-frequency (TF) analysis allows visualization of a signal's power spectrum as a function of time. In a TF plot, true HFOs are thought to be represented by an island of increased power at high frequencies, with the high power occurring within a distinct band (Figure 3A,B), while sharp, artifactual transients exhibit high power across all frequencies (Figure 3C).[34] Moreover, an HFO superimposed on a spike may have a power spectrum peaking at both low and high frequencies (Figure 3D).[34, 60] Application of a bandpass filter to the data, which is commonly the first step of HFO detection, is like taking a smaller horizontal slice of the TF plot. When this is done, all the examples in Figure 3 (including the artifact) will produce HFO-like events. Thus, examination of the TF plot can be used to distinguish real HFOs from false positive detections, which is often not possible by looking at the bandpass filtered data. However, the TF decomposition is computationally intensive, so these methods are not used for initial detection. Rather, they are applied after an energy-based detector with high sensitivity.

Common methods to calculate the time-frequency decomposition include the Stockwell transform,[61, 62] Morse wavelet,[60] short-time Fourier Transform,[52, 56] discrete wavelet transform,[52] Gabor wavelet,[63, 64] and Morlet wavelet.[54, 65-70] TF analysis has been used for visual confirmation of automatically detected HFOs,[60, 67, 68] and this process has also been successfully automated.[52, 54-56, 62, 70] These automated methods commonly apply a threshold to the ratio between a predetermined high frequency power and low frequency power.[52, 55] TF decomposition is also used for analysis of HFO features, which can shed light on their morphology.[63-66]

### *2.3.3 Machine learning techniques*

Generally, machine learning methods involve extracting features of detected HFOs from a training set of data (generally a certain percentage of the data set) and using those features for classification. Initial detection is commonly done using a high sensitivity detector, such as the RMS detector.[71-73] There are two subcategories of machine learning. The first is *supervised machine learning* techniques that use labelled data, e.g., visually marked HFOs and background

segments, to train the algorithm; the optimized parameters are then used on the testing dataset. These techniques have been used to separate true HFOs from false HFOs,[51] classify HFOs as ictal or non-ictal,[71] and distinguish between resected and non-resected tissue.[13] Methods include neural networks,[51] logistic regression and K-nearest neighbors,[71] and support vector machines.[13, 71] In contrast, the second subcategory is *unsupervised machine learning* techniques that do not require visually marked data to train the algorithms. The algorithms cluster the initial detections based on their similarity to one another, either using features or the event itself. The optimal number of clusters can be chosen using various techniques.[16, 32, 72, 73] Based on the characteristics of their members, clusters can then be empirically interpreted as containing ripples, fast ripples, or false HFOs due to artifacts or sharp transients, thus improving detector specificity[32, 72, 73] or aiding classification of SOZ and non-SOZ channels.[16] All of these studies used Gaussian mixture models, sometimes in combination with other clustering algorithms.

## 2.4 Testing and validation of automated algorithms

After choosing methods for initial detection and rejection of false positives, the performance of an automated algorithm can be tested using an independent dataset. This procedure can be done using event-level validation techniques, clinical validation techniques, or a combination of both.

Event-level validation techniques can be used to verify the characteristics of detected events relative to visual detection or inspection:

(1) *Comparison to visual detection.* The most frequently used test for automated algorithms is to compare the automatically detected HFOs with those visually marked by two or more reviewers. This enables the calculation of detector sensitivity and specificity, and the goal is to achieve high overlap between automatic and visual detection, with the visually marked events treated as the ground truth. However, this procedure is time and labor intensive, and subject to the investigator bias inherent in visual detection.[28, 29]

(2) *Verification via visual review.* An alternative, when the dataset is very large, is to visually examine a random sample of the detected events, e.g., 2000 out of 1.5 million events [42] or

three out of 11 patients.[51] It is then possible to estimate the percentage of automatically detected events that resemble true HFOs or are false positives due to the filtering of artifacts or sharp transients. Here, the goal is to ensure that the number of automatic false positive detections is sufficiently low, and this procedure is less time intensive than comparison to visual detection. However, this again assumes that visual detection is the ground truth, despite its drawbacks. It is also not possible to know if the detector missed events (false negatives) or whether the detections are a representative sample of true HFOs.

Clinical validation techniques can be used to verify that the events detected by the automated algorithm are a biomarker of epilepsy:

(1) *Comparison to SOZ.* Detectors can be validated by identifying the channels with high ripple and/or fast ripple rates and comparing them with the clinically determined SOZ. This strategy is aimed at measuring the utility of automatically detected HFOs as an interictal biomarker of the SOZ. If the detection algorithm has been previously tested using visual detection or visual review, this serves as further validation of both the algorithm and the value of visually marked HFOs. If the algorithm has not undergone prior testing, there is no guarantee that the automatically detected events would have been visually marked. In this case, if significant differences between SOZ and non-SOZ channels is demonstrated, basic characteristics of the detected events (duration, frequency, amplitude, etc.) should be analyzed.

(2) *Comparison to surgical outcome.* Lastly, a detector can be validated by comparing its output, e.g., the HFO rate for each electrode, to the resected volume and seizure outcome after surgery. In these studies, it is common to analyze the R or FR "resection ratio," which denotes the percentage of brain regions exhibiting high HFO rates that were resected. In theory, patients with high resection ratios should have good surgical outcome. Here, the goal is to validate HFOs as a biomarker of the EZ. This form of validation has more clinical utility than comparison to the SOZ, as surgical removal of the SOZ does not always result in seizure freedom. However, there are significant limitations to interpreting outcome. Tissue beyond the HFO-generating regions is often resected, which limits interpretation of seizure free outcomes, and if the seizures persist, this may be because some HFO-generating regions were not

sampled. These studies also generally require more subjects, with integration of imaging and electrophysiological data and collection of long-term follow-up data. As with comparison to the SOZ, the features of automatically detected events will depend on whether the detector was previously tested using visual detection or review.

## 2.5. Parameter optimization

The automated methods in Table 1 involve the use of multiple inter-dependent parameters for initial detection and rejection of false positive detections. Changing these parameters can greatly affect the output of the detector.[74] Therefore, optimizing detector parameters is an important step in the implementation of an automatic detector. In order to achieve sufficient sensitivity and specificity, the parameters for initial event detection (Section 2.2) and rejection of false positive detections (Section 2.3) must be adjusted for each data set,[74] for each subject,[41] or for each channel of iEEG.[57] In that sense, these detectors are not fully automated.

To determine the optimum parameters, the steps described in this section are applied to a randomly selected subset of data[13, 47] or patients,[51, 55] sweeping through parameter values. The remaining, usually larger, subset is used for testing the detector performance. A hold-one-out method can also be used to select data for optimization and testing, especially when limited data are available.[42] During training, automatically detected events are visually inspected, or they are compared against visually marked events, the visually determined SOZ, or clinical outcome (see Section 2.4). The parameter set that gives the best results is then applied to the testing dataset to measure detector performance. Alternatively, it has been suggested that varying the detection parameters over a small range can be used to test the robustness of SOZ localization; if a channel has a high HFO rate for multiple sets of parameters, this suggests that the HFOs are easily separated from the background and increases confidence in classifying the channel as SOZ.[53]

It is important to note that the parameters used for automatic detection are inter-dependent. For example, if the energy threshold is decreased, the duration of the detected events will increase. Naturally, optimization becomes increasingly difficult when there are many inter-

dependent parameters. Therefore, it can be advantageous to use a detector that was designed to minimize the number of parameters, e.g., Charupanit et al.[57]

## 3. Comparison of automated detectors

Automated detectors are often validated on novel data sets, which are recorded at different centers with electrodes of different sizes, and detection can be implemented with varying parameters and frequency ranges. Therefore, directly comparing performance metrics of different detectors is challenging. Detectors can only be accurately compared when they are tested on the same dataset and the parameters for each detector are optimized for that dataset. Overall, we identified eight studies that compared their new detector to existing detectors on the same data set.

In particular, two studies compared detectors after implementing independent optimization procedures for the parameters of each detector. First, Zelmann, Mari, Jacobs[74] compared the MNI detector to the line length (LL)[30] and RMS detectors[33] on the same dataset used to optimize parameters for the MNI detector. In addition to using the parameters from the original papers for detection, the authors also optimized the parameters using a subset of the data and compared performance using the optimum values. When the original parameter values were used, the detectors performed very poorly relative to the performance stated in the original papers, but significant improvement was seen when using the optimized parameters. This emphasizes the importance of parameter optimization for detector performance. With optimum parameters, the MNI detector fared marginally better than the other two. However, the LL detector was originally made for a frequency range of 0.1 to 100Hz, while it was tested here for 100-500Hz. Second, Charupanit, Lopour [57] compared their detector to the RMS detector using the same dataset. The two threshold selection methods described in the paper (iterative and non-iterative) and the RMS detector performed comparably when optimization was done for all channels. The iterative method performed significantly better in a rigorous cross-validation test, where optimization was done on a subset of channels and testing was done across the remaining channels.

Gardner, Worrell, Marsh[30] compared their LL detector against the RMS detector, modifying it to suit the clinical dataset. The LL detector performed significantly better, but the parameters of the RMS detector were not optimized and it was not originally designed for use in the 0.1 to 100Hz frequency range. Cimbalnik, Hewitt, Worrell[48] compared their CS algorithm to the RMS and LL detector in a dataset including human, rodent, and canine recordings. They reported superior detection accuracy and temporal localization using their algorithm. Burnos, Hilfiker, Surucu[55] also compared their detector to the RMS and LL detector; in two patients, the detectors performed equally, while in the other four patients their detector did considerably better. Dumpelmann, Jacobs, Kerber [51] compared theirs to the LL detector, and ROC analysis showed that theirs was superior. Ren, Yan, Yu [40] compared their detector to the MNI, RMS, LL and Hilbert detectors. For both ripples and FRs their algorithm had significantly higher sensitivity and specificity. Similarly, Wu, Wan, Ding [32] found that their proposed detector performed better than five existing detectors. However, in all of these comparisons, the existing detectors generally performed worse than they did in the original publication. This may be due to three important limitations. First, the detector parameters were not always optimized prior to applying them to the new dataset. Second, detectors were sometimes tested on datasets or in frequency ranges that were entirely different from the ones they were designed for. Third, if visual marking from one center is used to create the gold standard for comparison, there may be unconscious bias toward the detector from that center, as those doing the manual marking may have knowledge of how that detector works.

## 4. Relationship between automatically detected HFOs and surgical outcome

Fifteen studies published between 2011 and 2019 used automatic detectors to relate the presence of HFOs to surgical outcome (Table 2). All studies were retrospective, except Jacobs et al.[41] Most studies used interictal HFOs recorded during slow wave sleep, although one study used ictal recordings[75] and two studies used intraoperative recordings.[62, 76]

In seven of the studies, previously validated algorithms were used to detect HFOs. Eight studies employed novel, unpublished automatic detectors, rather than using one of the externally

validated algorithms in Table 1. In each case, the algorithm parameters were optimized for the study's data set; this would ideally be done using a separate training dataset, but this information was not always provided. These novel detectors were typically combinations or variations of standard techniques, including RMS amplitude,[77] Hilbert envelope,[18] T-F analysis,[78] or machine learning methods.[13, 79, 80] In addition to the studies in Table 2, a considerable number of recent papers used visual markings to identify HFOs for analysis in post-surgical outcome. While this may suggest concern about the robustness of automated detection, multiple studies have reported that visual and automated detection produce similar results.[41, 62, 81]

Despite the wide variability in detection methods, results using automated algorithms have been relatively consistent. Two studies reported that complete resection of brain regions exhibiting high HFO rates correlated to good outcome, without separating them into ripple and fast ripple bands.[13, 82] Higher ripple resection ratios were frequently associated with improved surgical outcome,[18, 19, 62, 83, 84] and all of the studies that reported significant results for ripples also reported significance for fast ripples. However, two studies reported a significant link between HFO resection and surgical outcome only in the FR band.[19, 78] Generally, FRs were found to be a better indicator of surgical outcome,[18, 19, 62, 78, 83] although one study reported the opposite result,[77] and analyses of some larger datasets have not shown FR to be more specific than R.[41-43, 72] Other studies reported that that concurrent HFO and low frequency oscillations were a better marker than either alone,[79] and that a machine learning technique could be used to automatically rank and classify channels inside and outside the SOZ based on HFO rate.[80] The significance of HFOs as a predictor of outcome compared to spikes is not clear, as two studies reported conflicting results on this.[36, 56]

On the other hand, we found two studies reporting that removal of HFOs was not significantly correlated to surgical outcome[41, 76] The results of a meta-analysis[81] indicated that while nearly all studies found that increased R/FR resection increased seizure freedom post-surgery, this relationship was significant in only half of the studies. Moreover, the only prospective multicenter study in Table 2 reported non-significant results at a center level, where iEEG measurements used different recording techniques, even though there was correlation

between high HFO region resection and surgical outcome at a group level.[41] The results did not improve with visual detection. This may have been due to the analysis techniques used, the presence of physiological HFOs, under-sampling of the brain when recording iEEG, differences in types of epilepsy, or differences between chronic recording and intraoperative monitoring. It is also possible that HFOs are not specific to the EZ in all patients.

## 5. Discussion and Recommendations:

There are a wide range of challenges associated with HFO detection, the most prominent one being the lack of a strict physiological definition of an HFO. This precludes the development of a universally applicable detector. For every new project, researchers must choose a detector, optimize the parameters, and validate its performance. Drawing from the current literature reviewed here, we propose some general guidelines for this process, which are detailed below and summarized in Table 3.

*Which detection algorithm should be used?* Because the energy-based metrics for the detectors in Table 1 are correlated (Figure 2), the results of their initial detection will be comparable when optimal parameters are used. Evidence for this has come from studies comparing different detectors on the same data set (Section 3), which showed that once the detector parameters were properly optimized, the performance of the detectors was generally comparable. However, the results of the initial detection will include false positives due to artifacts and sharp transients. Therefore, implementation of false positive rejection methods may have a larger effect on the HFO rate than initial detection. In particular, methods based on the time-frequency decomposition are likely to be the most stringent. However, post-processing steps come at the cost of increasing the complexity of optimization, as more parameters are needed. Overall, the consistency of results using a wide range of detection methods suggests that choice of detection scheme is not critical; it is fine to use a simple technique, preferably one that has already been validated, as long as parameters are optimized for the dataset. In the future, more work is needed to understand the unique underlying physiology of HFOs, in order to guide development of more specific detectors.

*How should detector parameters be optimized?* All automated algorithms include parameters, such as a window size for the energy calculation and thresholds for amplitude, duration, and number of peaks. Some studies implement published detectors with fixed parameters. However, several studies have shown that proper selection of these parameters is a critical step in the detection of HFOs, and there are currently no recommendations for how this should be done. The parameters are often dependent on one another, and most studies have focused on optimization of the energy threshold relative to the background. However, all parameters should be varied over the widest possible range, and the best performance can be chosen using the Youden index of (sensitivity + specificity – 1).[70, 90] Then the selected values of all parameters should be reported along with the results. The optimal set of parameters is likely to be patient specific. For this reason, optimizing using small samples from each patient (e.g. use the first five minutes of data from each patient to select the parameters, then apply those parameters to the rest of the subject's data) may produce better results than optimizing based on a subset of patients (e.g. use all data from three subjects to select the parameters, then apply those parameters to the rest of the subjects). There is even some evidence to suggest that the parameter selection should be channel-specific.[57] It has also been suggested that a normalization pre-processing step to reduce the variance between data from different sources can provide more consistent detection results.[48] In the future, more work is needed to understand the robustness of HFO detection to changes in the parameters and recording setup and to develop automated patient-specific optimization techniques simple enough to be used in a clinical setting.

*How should a new detector be tested and validated?* After parameter optimization, the detector can be tested and validated via comparison to visually detected events, visual review of automatically detected events, comparison to the SOZ, and comparison to surgical outcome. One or more approaches may be chosen based on the specific goal of the study. Ultimately, validating an algorithm against the resected volume and surgical outcome is the clinical gold standard,[91] but if consistency with visually detected HFOs is desired, the output of the algorithm should first be tested against visual marking or visual review. For all methods, the validation should be done on an independent dataset that was not used for parameter

optimization. In order to robustly validate an algorithm, the detectors and parameters should be consistently applied across studies. We found many examples of detectors validated on one type of data (or in one frequency band) being used without optimization in a different setting, and it is not uncommon for a study to use a variation of an existing detector without repeating the validation. This has led to a myriad of different detectors, making comparisons between studies almost impossible. In the future, comparing new detection methods directly to a well-understood benchmark algorithm using the same dataset can help alleviate this problem, and authors should make the code for the new algorithm freely available. If the two algorithms perform comparably, use of the previously published algorithm is preferable. Similarly, when comparing HFO detection to the SOZ or surgical outcome, using multiple detection algorithms and varying detection parameters can help verify that the results are robust to these changes.

*How much data should be used for detection?* While initial HFO studies used only a few minutes of data per patient, due to the laborious nature of visual HFO marking, the use of automated algorithms enables analysis of larger datasets. Anti-seizure medications and the occurrence of seizures will affect HFO rates, so it is important to perform HFO detection on multiple, independent segments of data. It is currently standard practice to use interictal data collected during slow wave sleep. Short segments of data can be clipped periodically overnight, at least one hour away from any seizure, collected from multiple nights if possible.[78, 92] When reporting the results, an analysis of the variability of the measurements over time can be included. In the future, more work is needed to understand the stability of SOZ localization as a function of the dataset length, and characteristics of HFOs recorded during wakefulness should be explored.

*How can a threshold for the HFO rate be chosen?* After detection and the calculation of HFO rate for each channel, a threshold must be chosen above which the HFO rate is deemed pathological. For a given patient, the goal of this process is to identify any subset of channels with anomalously high rates. In theory, brain regions with HFO rates exceeding this threshold are potential surgical targets. This is not a trivial task, as the overall HFO rates and differences between epileptogenic and non-epileptogenic regions are patient-specific. Large clinical studies have shown that the variability of HFO rates between patients is too variable to establish a universal threshold for HFO levels,[15, 93] and there is no guarantee that the channel with the

highest HFO rate is abnormal.[72] Differences in rate can also occur due to the presence of physiological oscillations, different electrode types[11] (but see also[94]), and different types of epilepsy. Several automated methods have been proposed. One commonly used method is to assume that HFO rates exceeding a pre-determined rate (usually empirically determined) are pathological.[62] Others include Kernel Density Estimation,[42] Kittler's method,[18] Tukey's upper fence,[68] and the half maximum method.[55] In the future, additional development of patient-specific optimization techniques is needed. Because the determination of a threshold for HFO rate is directly tied to the HFO detection technique and its specificity, the methods for accomplishing these two tasks will need to evolve together.

*Are there alternatives to the discrete measurement of HFO rate?* Although the literature on HFOs is dominated by discrete detection of HFO events and the use of rate as a biomarker for the SOZ, several alternatives have been proposed. Some studies have suggested measures that can be applied to the entire high frequency signal, rather than detecting discrete events. For example, it was reported that the skew in the distribution of power values was higher in the SOZ compared to non-SOZ for three frequency bands (5-80Hz, 80-250Hz, 250-500Hz).[95] Other studies have measured cross-frequency coupling of high frequency amplitude with the low frequency phase (delta and theta bands), generally quantified by the modulation index (MI). A recent study in 76 patients showed significantly higher MI z-score in the SOZ compared to regions outside the SOZ.[96] Further, a multi-variate logistic regression analysis found that the model predicted outcome better in 123 patients when MI was included as a variable. Guirgis et al.[97] used eigenvalue decomposition of MI values to delineate a "region of interest" and found that when this region was spared during surgery, patients were less likely to be seizure free. Weiss et al.[98] found that coupling between high gamma (80–150 Hz) amplitude and slow wave (1-25Hz) phase was higher in the "ictal core" (territories that were fully recruited to the seizure) compared to the periphery, which could potentially aid in more precise localization of cortical regions for epilepsy surgery. Lastly, Ibrahim et al.[99] found that coupling between high frequency amplitude and theta and alpha phase was significantly elevated in the SOZ compared to non-epileptic regions. It should be noted that three of these studies[97-99] used ictal data, which is more challenging to collect and analyze than interictal data.

Functional and effective connectivity networks based on high-frequency data are also being investigated. Zweiphenning et al.[100] calculated network connectivity via short-time direct directed transfer function for different frequency bands. In patients with good surgical outcome, the total strength and net strength of outgoing propagations in the gamma and ripple bands was higher in electrodes within resected tissue compared to electrodes in tissue that was spared. An earlier study done by the same group found local enhanced connectivity of channels showing epileptiform events in the FR-band functional network.[101] They hypothesized that these hubs might cover the HFO-generating networks and their resection might lead to better outcome. González Otárula et al.[102] found a network organization of interictal HFOs which suggested that the resection of the source channels may be necessary for seizure freedom. However, in their dataset, the resection of the source channels was not significantly better than resection of channels with highest HFO rates.

There are advantages to metrics derived from continuous high frequency activity, compared to those based on detection of discrete HFOs. These metrics are not limited by the lack of a consensus on characteristic HFO features. Moreover, because these approaches generally do not define the semiology of individual events, they typically require fewer parameters, thus making patient-specific parameter optimization easier. Also, calculating metrics based on continuous activity may require less computation time than detecting discrete HFOs. Further research into these methods is needed to assess the efficacy of continuous high frequency activity as a biomarker of the SOZ.

Other HFO characteristics, including amplitude, duration, and peak frequency are potential alternatives to rate as a marker of the SOZ. Malinowska et al.[103] found that, in addition to HFO rates, HFO amplitudes and frequencies significantly differed between SOZ and non-SOZ in ictal, non-ictal and pre ictal periods. Pail et al.[25] found that both ripple and fast ripple durations were shorter in the SOZ than outside it, and the relative HFO amplitudes were also higher in the SOZ. Charupanit et al.[37] identified anomalous high frequency activity that stood out from the background and found that while the rates of these events were similar in and outside the SOZ, there was a significant difference in the amplitudes between the two regions.

Overall, the results using automated HFO detection for determination of the SOZ and comparison to surgical outcome are promising, and these techniques are gradually becoming accepted as robust and reliable. They make it possible to analyze large amounts of data very quickly. Standardized practices for the implementation and optimization of detectors will facilitate comparisons across multiple studies and identification of generalizable trends, which will lead to more rapid advancements in the clinical use of HFOs.

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## Conflict of Interest Statement

None of the authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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## Figures

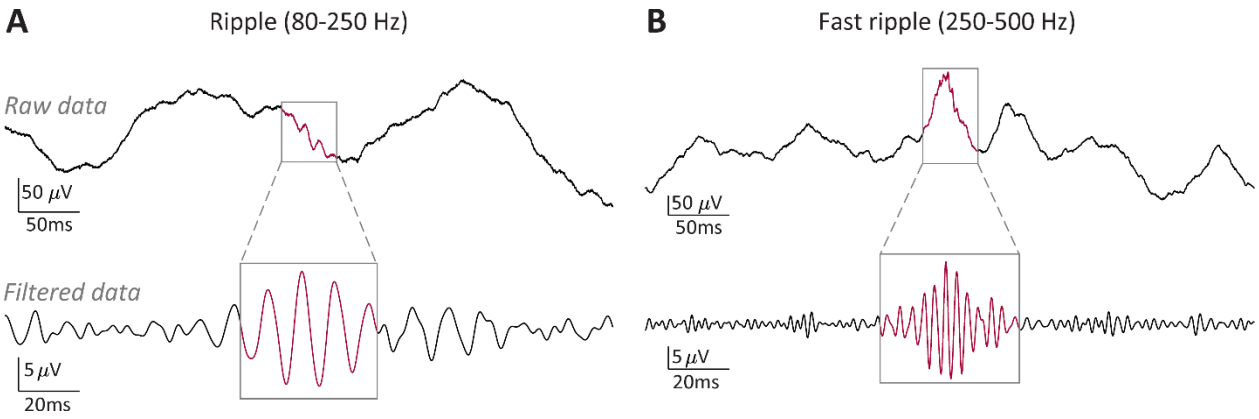


**Figure 1.** HFO examples (gray boxes). **(A)** Ripples consist of oscillations in the 80-250 Hz frequency band, and **(B)** fast ripples contain oscillations in the 250-500 Hz frequency band. The events are barely visible in the broadband data (top), but clearly stand out from the background when a band-specific filter is applied (bottom). Depth electrode recordings are from the amygdala (ripple) and anterior cingulate (fast ripple) of an 18-year-old male.

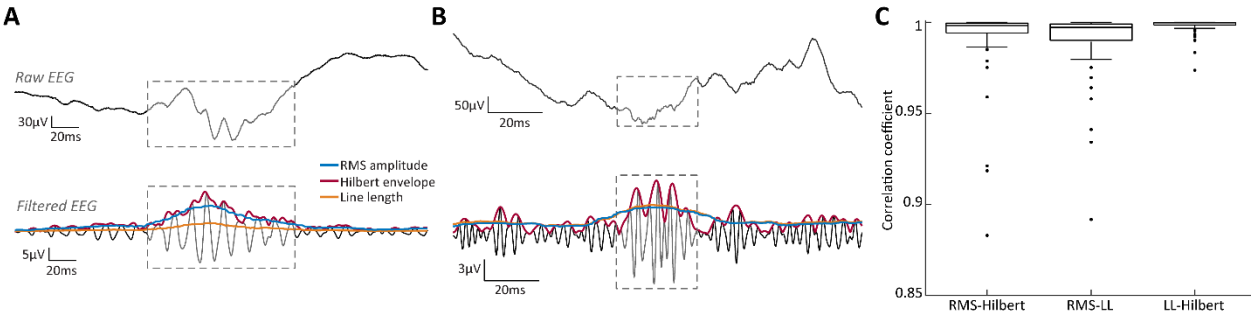


**Figure 2.** Energy measures used for HFO detection are highly correlated. Measurements of RMS amplitude (blue), Hilbert envelope (red), and line length (orange) are shown for **(A)** a representative ripple, recorded from the left anterior cingulate and **(B)** a representative fast ripple, recorded from the right anterior hippocampus. Depth electrode recordings are from an 18-year-old male. Line Length has been multiplied by a factor of five to aid visual comparison to the other measures. **(C)** The correlation between all three energy measures is high. Correlation coefficients were calculated between pairs of energy measures for 100 randomly selected data segments containing HFOs after bandpass filtering between 80-500 Hz.

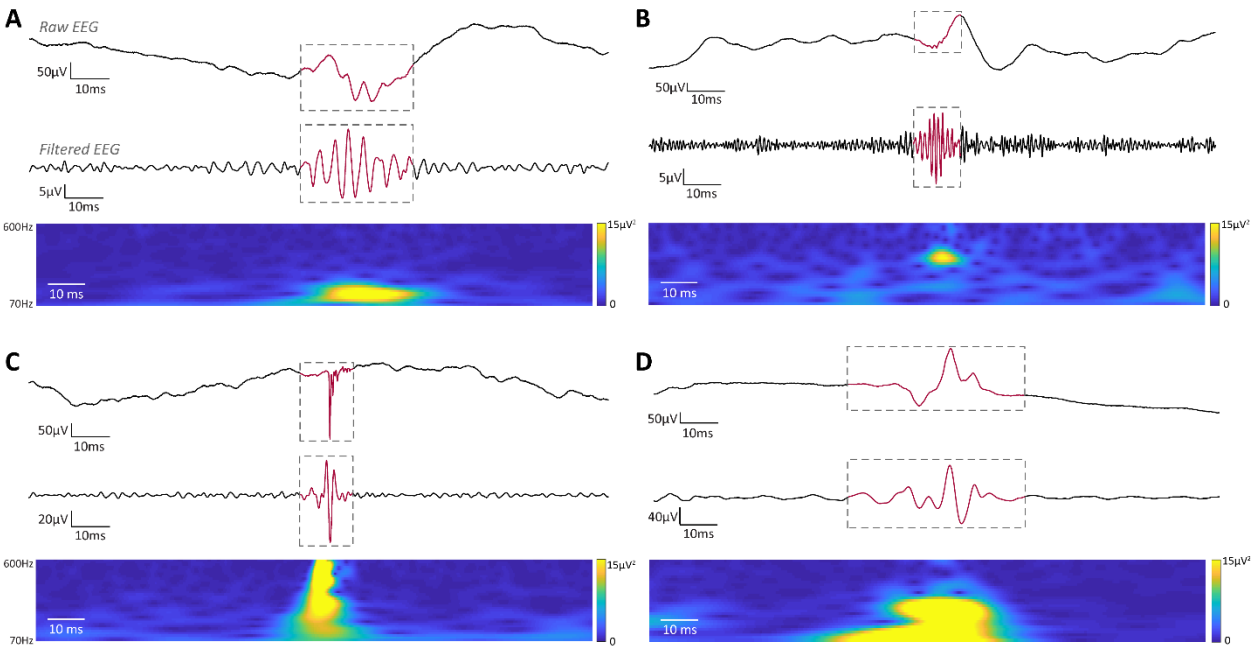


**Figure 3.** Time-frequency analysis can be used to distinguish between HFOs and sharp transients. Representative examples are shown for **(A)** ripple, recorded from supplementary motor area, **(B)** fast ripple, recorded from left anterior cingulate, **(C)** an artifact consisting of a narrow, high amplitude spike, recorded from the right posterior hippocampus and **(D)** an epileptiform discharge with an embedded ripple, recorded from left anterior hippocampus. Depth electrode recordings are from an 18-year-old male. In each subfigure, the top trace is the broadband iEEG signal, the middle trace is the 80-500 Hz filtered signal, and the bottom shows the time-frequency decomposition based on Morse wavelets. The events have similar morphology in the bandpass filtered data, but the time-frequency decompositions are unique.

*Table 1: Automatic Detection Algorithms*

Abbreviations – RMS: root-mean-square, T-F: time-frequency, T: Threshold, L: Window Length, D: Minimum duration, P: Minimum number of peaks, S: Minimum separation between distinct events, LF: Low frequency, HF: High frequency, LT: Low Threshold, HT: High Threshold, Nw: Number of wavelets, Ni: Number of iterations, GA-MP: Gabor atom – Matching Pursuit. Depth electrodes include any listed as depth macroelectrodes or stereotactic EEG in the original publication, while subdural refers to grids or strips on the cortical surface. Recordings were extraoperative without anesthesia, unless denoted as intraoperative. Validation methods include (1) Visual detection, consisting of direct comparison of automatically and visually identified HFOs, (2) Visual review, in which experts visually review automatically identified events, and (3) Comparison to SOZ to test whether or not high HFO rates are specific to the SOZ.

| Reference | Electrode type (Referencing) | Frequency range | Energy Measure (Parameters) | Artifact Rejection (Parameters) | Validation |
|---|---|---|---|---|---|
| **Staba 2002** | Depth, micro (not reported) | 100-500Hz | RMS Amplitude (Tx2, L, D, P, S) | None | Visual review |
| **Zelmann 2010** | Depth (not reported) | 80-450Hz | RMS Amplitude (T, D, S), informed by wavelet entropy baseline detection (T) | None | Visual detection for HFOs and baseline (two reviewers) |
| **Blanco 2011** | Subdural, depth with micro-wires (not reported) | 100-500Hz | RMS amplitude (Tx2, L, D, P, S) | Events discarded if similar to local background estimated by a Gaussian mixture model; remaining events were clustered, artifact cluster was rejected | Comparison to SOZ |
| **Chaibi 2013** | Depth (not reported) | 80-500Hz | RMS Amplitude after Hilbert Huang transform (T, L, P) | None | Visual detection (two reviewers) |
| **Gliske 2016** | Depth (common average) | 100-500Hz | RMS Amplitude (T, L, D, P, S) | Fast transients, DC shifts (L, Tx2, D); Artifact in common average (Tx2, L, D, P, S) | Visual review (three reviewers) |
| **Wu 2018** | Depth (not reported) | 80-500Hz | RMS Amplitude (T, L, D, P) | Clustering algorithm using 4 features | Comparison to SOZ |
| **Liu 2018** | Subdural, depth (bipolar) | 80-500Hz | RMS amplitude (Tx2, L, D, P, S) | Event considered artifact if the number of zero crossings was greater than 10 (T); clustering using 3 features to isolate HFOs from other events | Comparison to SOZ |
| **Gardner 2007** | Subdural, depth (not reported) | 30-100Hz | Short term line length (T, L) | None | Visual detection and visual review |

| | | | | | |
|---|---|---|---|---|---|
| **Dumpelmann 2012** | Subdural, depth (not reported) | 80-344Hz | Mean of squared amplitude, short term line length, instantaneous frequency (T, D, S) | None | Visual detection (two reviewers) |
| **Birot 2013** | Depth (not reported) | 250-600Hz | Square of filtered signal tapered by Hanning window (T, L) | Two methods to test ratio of power between HF and LF bands (D, LF, T) | Visual detection (one reviewer) |
| **Crepon 2010** | Subdural, depth (bipolar) | 180-400Hz | Hilbert Envelope (T) | Peak in Morlet wavelet T-F decomposition | None |
| **Burnos 2014** | Subdural, depth (bipolar) | 80-500Hz | Hilbert Envelope (T, D, P, S) | Ratio of power between HF and LF bands (T, LF, HF) | Comparison to SOZ |
| **Liu 2015** | Not reported (not reported) | 80-500Hz | Median operator threshold based on the median of the standard deviation of filtered data (T, D) | Min/max duration; raw data crosses zero >10 times; K-means clustering based on 3 features (N, T, D) | Comparison to SOZ |
| **Charupanit 2017** | Depth (not reported) | 80-250Hz | Iterative procedure to estimate background amplitude and set threshold (T) | None | Visual detection (two reviewers) |
| **Wu 2017** | Subdural (not reported) | 80-250Hz, 250-600Hz | Two methods: (1) Signal power reconstructed by complex Morlet wavelet and Shannon entropy (T, D, Nw); (2) RMS amplitude deconstructed by the adaptive GA-MP algorithm (T, D, Ni) | None | Comparison to SOZ |
| **Ren 2018** | Subdural, depth- (bipolar) | 80-200, 200-500Hz | Distribution of ranges in filtered data (local max-min for adjacent peaks) to estimate background and select threshold (LT, HT, P) | None | Visual detection (three reviewers) |
| **Cimbalnik 2018** | Depth, micro (not reported) | 44-120Hz, 73-197Hz, 120-326Hz, 197-537Hz | Dot product of amplitude and frequency dominance (T, S) | Detection must exceed threshold for 5 features (Tx5) | Visual review (3 reviewers) |

*Table 2: Papers that relate HFOs and clinical outcome using automatic detection*

Abbreviations – FCD: focal cortical dysplasia, EMD: empirical mode decomposition, LFO: low frequency oscillation, FR: fast ripple, NA: not applicable (not tested), R: ripple, SVM: support vector machine. Depth electrodes include any listed as depth macroelectrodes or stereotactic EEG in the original publication, while subdural refers to grids or strips on the cortical surface. Recordings were extraoperative without anesthesia, unless denoted as intraoperative.

| Reference | No. of subjects | Electrode type (Referencing) | Frequency Range | Detector | Removal correlated to better surgical outcome? | | |
|---|---|---|---|---|---|---|---|
| | | | | | **R** | **FR** | **Comparison** |
| **Akiyama 2011** | 28 | Subdural, depth (bipolar) | R: 80-200<br>FR: 200-300 | New detector based on Hilbert transform + threshold | Yes | Yes | FR>R |
| | | *Other result: SOZ not correlated with seizure outcome.* | | | | | |
| **Cho 2014** | 15 | Subdural, some depth on suspected lesions (common electrode, Pz) | R: 60-200<br>FR: 200- 500 | New detector based on Crepon 2010 and Staba 2002;[33, 54] false positive detection using power and amplitude relative to background | Yes | Yes | R>FR |
| **van klink 2014** | 14 | Subdural (bipolar) | R: 80-250Hz<br>FR: 250-500Hz | Zelmann 2010;[47] parameters were optimized on training data; spikes were visually identified | No | Yes | FR>R |
| **Dian 2015** | 6 | Subdural (bipolar) | LFO: <80 Hz<br>HFO: 80-400Hz | New detector based on EMD and feature extraction for LFO and HFO; SVM to classify channels; used separate training and testing datasets | NA | NA | NA |
| | | *Other result: HFO+LFO more consistent than LFO or HFO alone; analyzed 3 subjects* | | | | | |
| **Sun 2015** | 4 | Subdural (not reported) | R: 80-250Hz<br>FR: 250-500Hz | New detector; Advanced source analysis software[85] | Yes | Yes | FR>R |
| **Fedele 2016** | 54 | Intraoperative subdural (bipolar) | R: 80-250Hz<br>FR: 250-500Hz | New detector; events exceeded threshold based on Stockwell entropy for a min time, confirmed using HF peak in Stockwell transform; multichannel analysis to reject events occurring broadly | Yes | Yes | FR>R |
| | | *Other result: In post-resection intraoperative ECoG, FRs have 100% PPV and Ripples have 100% NPV* | | | | | |
| **Fedele 2017** | 9 | Subdural, acquired with custom device and low noise amplifier (bipolar) | FR: 250-500 Hz | New detector; HFO detection and artifact rejection using Fedele 2016[86], with T-F analysis as in Burnos 2014[55] | NA | Yes | NA |
| **Fedele 2017** | 20 | Subdural, depth (bipolar) | R: 80-250Hz<br>FR: 250-500Hz | Burnos 2016[61], with baseline detected separately for FR and R | Yes | Yes | R more sensitive; FR more specific |
| | | *Other result: FRs co-occurring with ripples predict seizure outcome better than each individually (100% specificity)* | | | | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **van 't Klooster 2017** | 54 | Intraoperative subdural (bipolar) | R: 80-250Hz<br>FR: 250-500Hz | Zelmann 2010[47] optimized for ECoG bipolar data; artifacts visually detected | No | No | NA |
| | | *Other result: Presence of FRs in the post-resection ECoG, given incomplete removal of FRs based on pre-resection ECoG, indicated worse outcome. None for ripples.* | | | | | |
| **Liu 2017** | 1 | Subdural (not reported) | 80-500Hz | Liu 2016[73] | NA | NA | NA |
| | | *Other result: HFOs provided more localized SOZ than spiking activity.* | | | | | |
| **Jacobs 2018** | 52 | Chronic depth or intraoperative subdural (not reported) | R: 80-250Hz<br>FR: 250-500Hz | Zelmann 2010[47]; 3 patients were used for training detector at each center | No | No | NA |
| | | *Other result: At an individual level, no reliable prediction could be made about outcome using HFOs* | | | | | |
| **Cuello-Oderiz 2018** | 21 | Depth; patients with FCD (bipolar) | R: 80-250Hz<br>FR: > 250Hz | von Ellenrieder 2016[89]; parameters optimized using first one minute of data | Yes | Yes | * |
| | | **Other result: R and FR had same specificity, but FRs had lower false positive rate* | | | | | |
| **Cimbalnik 2018** | 90 | Subdural, depth (not reported) | 65-600Hz | New detector; physiological and pathological HFOs detected separately. Multiple feature cascade detector, trained and validated on separate data sets | NA | NA | NA |
| | | *Other result: Failure to resect high HFO rate regions associated with poor outcome.* | | | | | |
| **Sumsky 2019** | 14 | Subdural, depth (common average) | >80Hz | New detector; Gliske 2016[42] plus SVM classifier based on HFO rate to identify SOZ channels | NA | NA | NA |
| | | *Other result: The method predicted the resected volume only in cases with good post-surgical outcome* | | | | | |

***Table 3**. Recommendations for implementation of automated HFO detection algorithms*

| |
|---|
| ***Which detection algorithm should be used?*** |
| • Initial detection is likely to be similar across algorithms; simple, previously validated algorithms are preferred |
| • Rejection of false positive detections due to artifacts is crucial; methods can be based on time domain properties, the TF decomposition, or machine learning |
| ***How should detector parameters be optimized?*** |
| • Vary all parameters over the widest possible range; choose the combination with the best performance |
| • If possible, optimize parameters for each subject using a subset of reserved data |
| • Report all parameters values when publishing results |
| ***How should a new detector be tested and validated?*** |
| • Both event-level validation techniques (to verify the characteristics of detected events) and clinical validation techniques (to verify that the detected events are a biomarker of epilepsy) are needed |
| • Event-level validation techniques: |
| – To maximize overlap between automatic and visual detection, compare to visually detected events |
| – To ensure minimal false positives in a large dataset, perform visual review of automatically detected events |
| • Clinical validation techniques: |
| – To test detected events as an interictal biomarker of the SOZ, compare to clinically-defined SOZ |
| – To test detected events as an interictal biomarker of the EZ, compare to surgical outcome |
| • Use independent datasets for parameter selection and validation |
| • Compare directly to results using a validated benchmark algorithm |
| • Make code for the algorithm freely available |
| ***How much data should be used for detection?*** |
| • Standard practice is to use interictal data during slow-wave sleep |
| • Analyze as much data as possible, at least multiple independent segments for each subject |
| ***How can a threshold for the HFO rate be chosen?*** |
| • Kittler's method, Tukey's upper fence, kernel density estimation, and the half maximum method have been successfully implemented |

- Selection of threshold for HFO rate is intertwined with choice of detection algorithm