Patient-specific optimization of automated detection improves seizure onset zone localization based on high frequency oscillations

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Abstract

High frequency oscillations (HFOs) are a promising biomarker of epileptogenicity, and automated algorithms are critical tools for their detection. However, previously validated algorithms often exhibit decreased HFO detection accuracy when applied to a new data set, if the parameters are not optimized. This likely contributes to decreased seizure localization accuracy, but this has never been tested. Therefore, we evaluated the impact of parameter selection on seizure onset zone (SOZ) localization using automatically detected HFOs. We detected HFOs in intracranial EEG from twenty medically refractory epilepsy patients with seizure free surgical outcomes using an automated algorithm. For each patient, we assessed classification accuracy of channels inside/outside the SOZ using a wide range of detection parameters and identified the parameters associated with maximum classification accuracy. We found that only three out of twenty patients achieved maximal localization accuracy using conventional HFO detection parameters, and optimal parameter ranges varied significantly across patients. The parameters for amplitude threshold and root-mean-square window had the greatest impact on SOZ localization accuracy; minimum event duration and rejection of false positive events did not significantly affect the results. Using individualized optimal parameters led to substantial improvements in localization accuracy, particularly in reducing false positives from non-SOZ channels. We conclude that optimal HFO detection parameters are patient-specific, often differ from conventional parameters, and have a significant impact on SOZ localization. This suggests that individual variability should be considered when implementing automatic HFO detection as a tool for surgical planning.

Introduction

For patients with medically refractory epilepsy, surgical resection of the epileptogenic zone (EZ) offers the potential to eliminate the occurrence of seizures (Schuele and Lüders 2008; Noachtar and Borggraefe 2009). However, the EZ remains a largely theoretical construct, as there are no biomarkers that enable identification of this brain region (Ryvlin et al. 2014; Kovac et al. 2017). Current clinical practice aims to identify the seizure onset zone (SOZ), currently the best proxy of the EZ, during the patients' pre-surgical evaluation. However, only 50-60% of patients are seizure free following resective surgery, emphasizing the need to improve localization of the EZ (Edelvik et al. 2013).

Over the past two decades, there has been growing interest in studying electrographic events called high-frequency oscillations (HFOs) as potential biomarkers of the EZ. HFOs are generally defined as spontaneous EEG patterns that consist of at least four oscillations with frequency > 80 Hz that clearly stand out from the background activity (Bragin et al. 1999). Interictal HFOs have a demonstrated association with the SOZ, as they occur more frequently at the site of seizure onset (Jacobs et al. 2012; Zijlmans et al. 2012). Moreover, the removal of HFO-generating regions has been correlated with good post-surgical outcome (Wu et al. 2010; Jacobs et al. 2010; Akiyama et al. 2011). It was also demonstrated that HFOs are not specific to brain lesions, further strengthening its case as a marker of epileptogenic tissue rather than other pathologic tissue changes (Jacobs et al. 2009). However, despite its potential as a biomarker of the EZ, HFO analysis has not yet proven to be reliable in individual patients (Roehri et al. 2018; Jacobs et al. 2018).

One factor that contributes to individual patient reliability of HFO analysis is the method of detection. Automatic HFO detection algorithms are increasingly viewed as a critical step to translating the analysis into clinical practice (Worrell et al. 2012), but there are no broadly accepted standards for their implementation. Such detection algorithms are developed using a specific frequency band, location of the brain, and/or electrode type (Sindhu et al. 2020). When they are subsequently applied to a new dataset,

the parameter values are often chosen to match the original publication, in order to provide independent validation of the algorithm's utility, promote reproducibility of results, and to avoid overfitting to the data. However, the use of such standard configurations leads to suboptimal performance when used for a different data set or frequency range. For example, when previously published algorithms are implemented without optimizing the parameters, they exhibit lower detection accuracy (relative to visually detected events) than originally reported (Gardner et al. 2007; Dümpelmann et al. 2012; Cimbálník et al. 2018; Ren et al. 2018). Consistent with this, several studies have demonstrated that HFO detection accuracy relative to visually marked events can be improved by optimizing the algorithm parameters (Zelmann et al. 2012; Chaibi et al. 2013; Charupanit and Lopour 2017).

This evidence supports optimization of HFO detection parameters; however, from a clinical perspective, there are two important questions that remain unanswered: First, does optimization of HFO detection parameters improve localization of the SOZ? Although optimization improves accuracy relative to visually detected HFOs, this does not guarantee that the improvement will be clinically meaningful for surgical planning. In two studies, SOZ localization accuracy based on HFO rate was poor when previously validated algorithms were applied to a new dataset without optimization (Burnos et al. 2014; Wu et al. 2018). However, because the algorithms were not optimized and re-tested, it is unknown whether this would have improved their performance. Second, if optimization improves SOZ localization, does the parameter selection need to be patient-specific? In clinical studies relating resection of HFO-generating tissue to surgical outcome, it is standard for the same detection parameters to be applied to all patients (Fedele et al. 2017; Jacobs et al. 2018). Therefore, answering this question is crucial for the design of future clinical trials.

To answer these questions, we used a frequently cited automatic detector and two independent datasets to measure the SOZ localization accuracy based on a wide range of HFO detection parameters. We did this independently for each subject, allowing us to estimate the best possible localization accuracy based on HFO rate, assuming that an optimization procedure had been used to select the detection parameters. We

also measured the improvement in localization accuracy when using patient-specific detection parameters versus the fixed, conventional values. Our goal was to investigate the impact of optimization on the accuracy of SOZ localization, assess the variation in results across patients, and identify the algorithm parameters most critical to the optimization procedure.

Methods

Clinical data collection

Twenty patients with medically refractory epilepsy from two medical centers were identified retrospectively and included in this study. Seven of these patients underwent implantation of intracranial electrodes for presurgical evaluation from June 2015 to March 2017 at the University of California, Irvine (UCI) Medical Center. We will refer to this as the UCI dataset. We included only patients with a postoperative outcome of Engel Class I, which suggests that the clinical SOZ localization was successful. For each patient, the SOZ was defined as electrodes involved within the first three seconds of seizure onset, based on visual assessment of the ictal intracranial EEG (iEEG). If patients had multiple seizures with different regions of onset during recording, all SOZ channels were considered SOZ. The demographic and clinical characteristics of these patients are shown in Table 1. Collection and analysis of retrospective patient data for this study was approved by the Institutional Review Board of the University of California, Irvine.

Table 1. Patient demographics of the UCI dataset. Abbreviations: AM = amygdala; AH = anterior hippocampus; depth = depth electrode; FLE = frontal lobe epilepsy; grid = subdural grid electrode; HH = head of hippocampus; HP = hippocampus; L = left; MF = mesial frontal; PFC = pre-frontal cortex; TH = tail of hippocampus; TLE = temporal lobe epilepsy; R = right

Patient	Age, Gender	Seizure semiology	MRI	Diagnosis	Electrodes	SOZ channels	Surgery	Engel outcome	Postoperative follow-up (months)
1	44, M	Complex Partial Seizures	Cortical Dysplasia in PFC	FLE	1 grid 8x8 2 grid 2x8 1 grid 4x8	RMF28-32	R Frontal Lobectomy	IA	47
2	50, M	Complex Partial Seizures	White matter changes in frontal lobe; possible right mesial temporal atrophy	TLE	5 depth 1x16	RAH5-8	R Temporal Lobectomy	IB	22
3	46, M	Complex Partial Seizures	Right Hippocampal Sclerosis	TLE	5 depth 1x16	RAH4	R Temporal Lobectomy	IA	41
4	34, M	Complex Partial Seizures	Bilateral hippocampal abnormalities with mild left-sided atrophy	TLE	2 depth (1x14) 3 depth (1x16) 2 grid (2x6) 1 depth (1x10)	RAM1-2, RHP1-3	R Temporal Lobectomy	IA	2
5	57, F	Complex Partial Seizures	None	TLE	11 depth (1x10) 1 depth (1x12)	LHH1-3, LTH2-3	L Lateral Temporal Lobectomy, L Amygdala and Hippocampal Resection	IA	23
6	53, F	Complex Partial Seizures	Left Mesial Temporal Sclerosis	TLE	10 depth (1x10)	LTH1	L Temporal Lobectomy	IA	32
7	54, F	Complex Partial Seizures	None	TLE	10 depth, (1x10)	RHH1-4, RAM1-2	R Temporal Lobectomy	IB	26

The remaining thirteen patients included in this study were obtained from the freely available online database associated with Fedele et al. (2017) at iEEG.org (http://crcns.org/data-sets/methods/ieeg-1/about-ieeg-1). These patients underwent invasive EEG recordings with subdural and/or depth electrodes from March 2012 to April 2016 at the University Hospital Zurich as part of their presurgical evaluation. We refer to these thirteen patients as the ETH Zurich dataset. We included all patients that reported good clinical outcomes (class 1) at least 1 year following resective surgery based on the International League

Against Epilepsy (ILAE) scale. Information regarding electrode types, data acquisition, and sleep scoring can be found in Fedele et al. (2017). Patient demographics for the ETH Zurich dataset are in Table 2.

Table 2. Patient demographics of the ETH Zurich dataset. Abbreviations: depth = depth electrode; ETE = extratemporal epilepsy; ILAE = International League Against Epilepsy; Les = lesionectomy; sAHE = selective amygdala hippocampectomy; strip = strip electrode; TLE = temporal lobe epilepsy

Patient	Age, Gender	Epilepsy	Type of electrodes	Number of channels in resected tissue	Number of channels in non-resected tissue	Surgery	ILAE outcome	Postoperative follow-up (months)
8	25, M	TLE	5 depth 1 strip 4 x 1 1 strip 6 x 1	9	14	sAHE; Les	I	12
9	33, M	TLE	8 depth	12	12	sAHE; Les	I	29
10	20, F	TLE	5 depth	12	3	sAHE	I	13
11	20, F	TLE	8 depth	12	12	sAHE	I	41
12	40, M	TLE	8 depth	12	12	sAHE	I	14
13	48, M	TLE	8 depth	12	12	sAHE	I	11
14	37, M	ETE	1 grid 8 x 4 2 strips 4 x 1	3	31	Les	I	36
15	36, M	ETE	1 grid 8 x 8 1 depth	3	62	Les	I	37
16	49, M	ETE	1 grid 8 x 4 1 depth	21	16	Les	I	25
17	17, M	ETE	1 grid 8 x 8 1 depth	3	50	Les	I	25
18	46, F	ETE	2 grids 8 x 2 1 strip 6 x 1 1 strip 4 x 1 1 depth	1	29	Les	I	10
19	31, F	ETE	1 grid 8 x 4 2 strips 4 x 1	4	23	Les	I	25
20	17, F	ETE	1 grid 8 x 4 1 depth	3	34	Les	I	19

Data acquisition

Intracranial EEG was recorded for each patient using a combination of subdural electrocorticogram (ECoG) grids and strips, as well as depth electrodes. Recordings from the UCI dataset were collected using a Nihon Kohden JE-120A amplifier with a minimum sampling frequency of 2000 Hz for all patients. Recorded data were re-referenced to a bipolar montage for analysis. All bipolar re-referenced

channel pairs that included an SOZ channel were deemed as SOZ (for example, channels RAH3-4 and RAH4-5 of UCI patient 3 were considered SOZ). Five 3-minute epochs from one night of iEEG recording were randomly selected for each UCI patient, for a total of 15 minutes per patient. Each epoch was chosen from data recorded between 8pm and 8am to improve the likelihood of analyzing sleep data, as HFO rates are increased and the occurrence of muscle artifacts is reduced during slow-wave sleep compared to wakefulness (Clemens et al. 2003; Staba et al. 2004; Bagshaw et al. 2009). We confirmed that all epochs were interictal data, recorded at least 1 hour away from seizures to reduce the influence of seizures on HFOs (Pearce et al. 2013). We analyzed all implanted electrodes, which ranged from 80 to 128 contacts for each UCI patient.

All interictal recordings from the ETH Zurich dataset were obtained at least 3 hours away from seizure activity, and we analyzed five 5-minute epochs of slow wave sleep from one night of recording. We included the same channels used for analysis by the original authors; the included and excluded channels can be found in the supplementary information provided by Fedele et al. (2017). Of note, the number of analyzed channels for each patient ranged from 15 to 53. For the analysis in the current study, we will define the "SOZ channels" to be the bipolar re-referenced channels within the resected area for each patient; the specific sites of seizure onset within the resected area were not provided. Defining the SOZ based on the resected volume will likely overestimate the true SOZ in the ETH Zurich dataset, while the method used for the UCI dataset is likely an underestimate due to limited sampling of brain tissue using iEEG electrodes. These datasets are therefore complementary and represent the full range of possible SOZ definitions.

Data processing

Automatic HFO detection

Automated HFO detection was performed using an algorithm based on the root-mean-square (RMS) amplitude of bandpass filtered data (Staba et al. 2002). We will refer to this as the RMS detector. We used the RMS detector because it is referenced often as a benchmark for new algorithms (Gardner et al. 2007; Zelmann et al. 2012; Charupanit et al. 2020), serves as the core of many other detectors (Blanco et al. 2010; Zelmann et al. 2010; Chaibi et al. 2013; Burnos et al. 2014; Gliske et al. 2016; Wu et al. 2018), and is algorithmically simple to implement and examine. In this algorithm, broadband data is bandpass filtered in the 100-500Hz frequency range, and candidate events are identified when the RMS of the bandpass filtered signal exceeds a threshold for a minimum duration (which we will abbreviate as "min_dur;" see Fig. 1a). The RMS signal is calculated using a moving window ("RMS_win"), and the first threshold ("nSD1") is defined as five standard deviations above the mean RMS signal. Consecutive events separated by less than a predefined gap time ("gap") are combined into one event. Candidate events are retained when a minimum number of peaks ("min_pk") in the rectified filtered data exceed a second threshold ("nSD2") defined as 3 standard deviations above the mean rectified data.

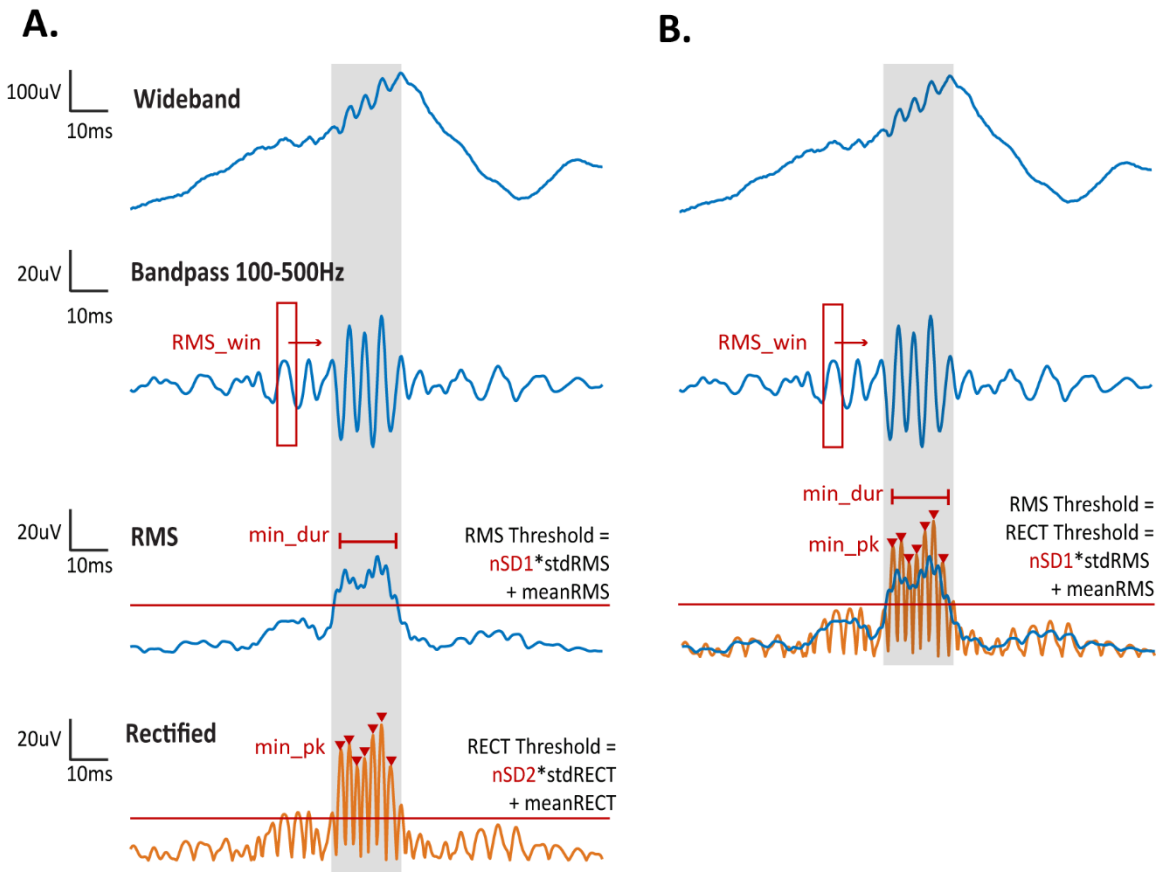

Figure 1. *Automatic HFO detection algorithm. (A) Full RMS detector and (B) Reduced RMS detector used in our analysis. The shaded gray region represents the window containing the identified candidate event. Detection thresholds are indicated by horizontal red lines, and each peak in the candidate event is marked by a red triangle. Abbreviations: RMS = root-mean-square, std = standard deviation*

To reduce algorithmic complexity and minimize the number of parameters to be optimized, we simplified the RMS detector algorithm by modifying the threshold applied to the rectified data (Fig. 1b). We set threshold two equal to threshold one (nSD2 = nSD1), as they both ensure that the signal's energy exceeds a threshold determined from baseline activity. As in the original algorithm, we required that a minimum number of peaks in the rectified filtered data exceed this threshold, to promote rejection of fast transients. All other steps in the original algorithm were maintained.

The detection algorithm used in our analysis thus contains five parameters that must be considered during optimization: RMS window size (RMS_win), minimum event duration (min_dur), number of standard deviations above the mean RMS signal (nSD1), minimum gap time (gap), and minimum number of peaks (min_pk). From these parameters, we varied the three that directly affect initial detection of candidate events: RMS window size, minimum event duration, and threshold. Because the minimum gap time is a post-processing step to join candidate events and the minimum number of peaks has little impact as a criterion due to the redundancy with minimum event duration, we kept these variables constant at their default values. The default values of each parameter and values tested during the optimization procedure are described in Table 3.

Table 3. Detection parameters varied during optimization and corresponding ranges of values. Default values are underlined. The default value for minimum gap time is 10ms and minimum number of oscillations is 6

Parameter	Values
Threshold (nSD1)	1, 2, 3, 4, <u>5</u>, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15
RMS window size (RMS_win) (ms)	2, <u>3</u>, 5, 7, 9, 11, 15, 17, 20
Minimum event duration (min_dur) (ms)	<u>6</u>, 12

Automatic artifact rejection

Because the RMS detector is highly sensitive (Gardner et al. 2007), we implemented two artifact rejection methods to improve specificity: PopDet and BkgStabaDet. Both methods were introduced by Gliske et al. (2016) for the purpose of creating a generalized HFO detection algorithm for long-term intracranial EEG recordings, such that the algorithm automatically identifies quality HFOs without any patient-specific tuning or operator intervention (Gliske et al. 2016). These artifact rejection steps were designed using the RMS detector for initial detection, making them appropriate for our analysis. In this study, the default parameters from Gliske et al., 2016 were used for all patients and all parameter sets.

The popDet criterion was designed to detect DC shifts and fast transients commonly found in EEG data (Fig. 2a, b). When a DC shift or fast transient is filtered, it can have the appearance of an HFO in the 100-500 Hz frequency band (Bénar et al. 2010; Zelmann et al. 2010). However, these transients also contain power at very high frequencies, whereas a true HFO should have band-limited power. Therefore, the popDet identifies instances when the line length of a 0.1s window in the 850-990 Hz frequency range exceeds a threshold of 5 standard deviations above the mean line length calculated from baseline. Baseline is defined as a 5-second window preceding the window being evaluated.

The BkgStabaDet was designed to detect spatially diffuse HFOs, which are considered false positive detections because they contradict the idea that HFOs should be focal events (Bragin et al. 2002, 2011). If an HFO occurs in all channels of a depth electrode or grid, it will appear in the common average (Fig. 2c). Therefore, detections in a single channel that occurred within 100ms of a detection in the common average were excluded from further analysis. As in the Gliske et al. (2016) implementation, we applied the RMS detector from Staba et al. (2002) to the common average within each depth electrode or grid using the default parameters.

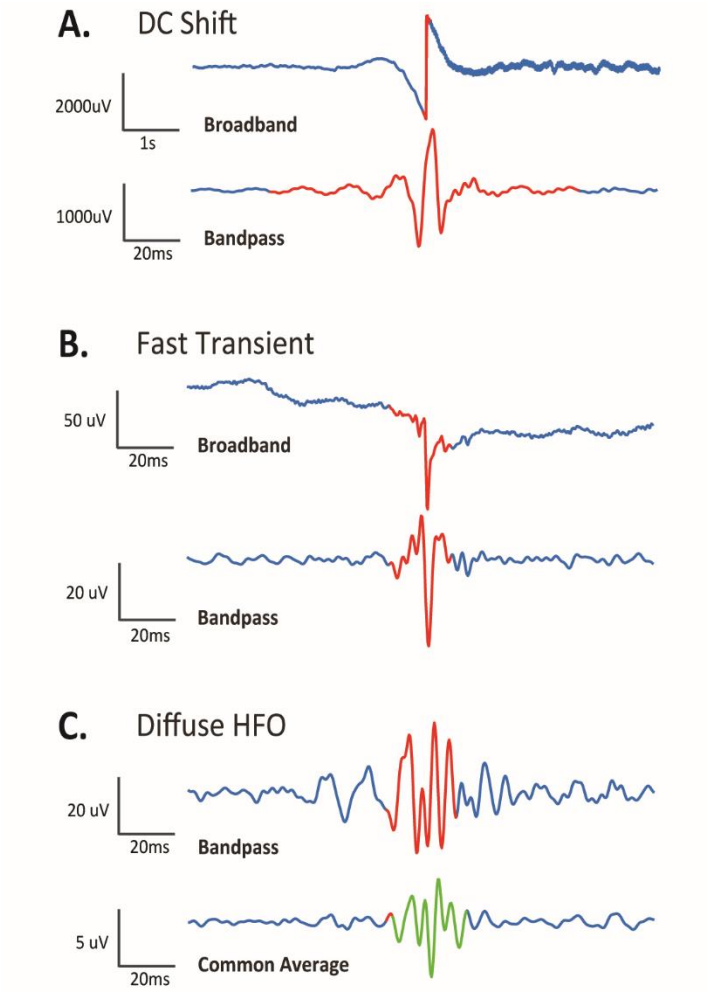

Figure 2. *Examples of rejected artifacts. (A) DC Shift in the broadband data (top) detected by popDet in the bandpass filtered data (bottom), and (B) fast transient in the broadband data (top) detected by popDet in bandpass filtered data (bottom), with the artifacts highlighted in red. (C) Diffuse HFO in the bandpass filtered data (top) detected by BkgStabaDet in the common average of the bandpass filtered data (bottom). The artifact (highlighted in green) represents the common average HFO that occurred at or near (±100ms) the same time as the detected HFO (highlighted in red) in the bandpass filtered signal.*

Data analysis

SOZ localization defined by rate thresholding

After HFO detection and artifact rejection were performed for a given parameter set, the HFO rate (number per minute) for each channel was averaged across epochs. A threshold was then applied to the

average HFO rates; channels with average HFO rates exceeding the rate threshold were classified as SOZ and the remaining channels were classified as non-SOZ (nSOZ).

Receiver operating characteristic curves and precision-recall curves

For each parameter set, we used a receiver operating characteristic (ROC) curve to characterize the ability of automatic HFO detection to localize the clinically-determined SOZ. For channels defined clinically as SOZ (based on visual interpretation of ictal iEEG), those with HFO rates that exceeded the threshold were marked as true positives (TP), and those that did not exceed the rate threshold were marked as false negatives (FN). For channels defined clinically as nSOZ, those that had HFO rates below the threshold were marked as true negatives (TN), and those with HFO rates above the threshold were marked as false positives (FP). The ROC curve was plotted by varying the HFO rate threshold and determining the true positive rate (TPR) and false positive rate (FPR) for each value:

$$\mathrm{TPR} = \frac{\mathrm{TP}}{\mathrm{TP+FN}} \qquad (1)$$

$$\mathrm{FPR} = \frac{\mathrm{FP}}{\mathrm{FP+TN}} \qquad (2)$$

The area under the ROC curve (which we will abbreviate AUC) and the optimum cutoff (defined as the minimum distance between the ROC curve and the top left corner) were determined for each parameter set for all patients.

As a complementary measure, Precision-Recall (PR) scores were evaluated to examine the positive predictive value for each parameter set. Precision-Recall analyses are preferred when prediction power of imbalanced classes is being evaluated; in our case, we have imbalanced classes represented by the small subset of SOZ channels compared to the larger class of nSOZ channels for UCI patients, and the small subset of nSOZ channels compared to the larger class of SOZ channels for some ETH Zurich patients (specifically, patients 10 and 16). Precision (P), Recall (R), and the F1 score (F1) were computed as follows:

$$P = \frac{TP}{TP+FP} \quad (3)$$

$$R = \frac{TP}{TP+FN} \quad (4)$$

$$F1 = 2\,\frac{P*R}{P+R} \quad (5)$$

Like the ROC curve, the PR curve was constructed by varying the rate threshold and calculating the precision, recall, and F1 score for each value. The optimal F1 score was defined as its maximum value, which represents the maximum harmonic mean of precision and recall. After calculating the ROC and PR results for each parameter set, the maximum AUC and optimal cutoff of the ROC curve, as well as the maximum AUC and optimal F1 score of the PR curve were determined for each patient.

Artifact counting

To assess the impact of the automated artifact rejection steps, we calculated the percentage of candidate HFOs rejected for each parameter set. The percentage of rejected candidates by popDet was calculated as the total number of candidates marked by popDet over the total number of candidates counted across all epochs. The same procedure was applied to candidates marked by BkgStabaDet. Because a candidate can be marked by both popDet and BkgStabaDet, the total percentage of rejected candidates by popDet and BkgStabaDet can exceed 100.

Results

Minimum event duration does not significantly impact SOZ localization

SOZ localization results were similar when HFO detection was done using minimum event duration (min_dur) values of 6ms or 12ms. We noted this pattern in all patients; one representative example is shown in Fig. 3, and additional examples can be found in Supplementary Fig. S1. Comparing the heatmaps in Figures 3a and 3b, the range of optimal F1 scores remained the same across the parameter

space, with the highest optimal F1 score achieved using a low threshold and short RMS window. A similar pattern of optimal parameters occurred in the AUC values. Because doubling the minimum event duration did not significantly alter localization results for any patient, the remaining results are reported using only a minimum event duration of 6ms, which was the value used in the original publication.

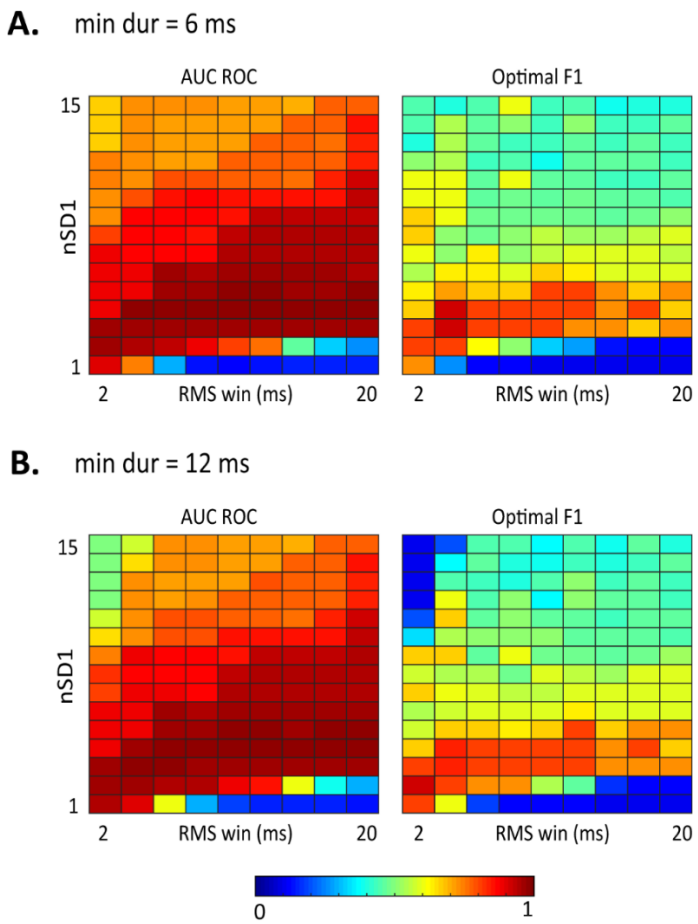

Figure 3. *Minimum event duration does not affect SOZ localization performance. Representative examples of SOZ localization performance across the parameter space, comparing results calculated using minimum event duration of (A) min_dur=6ms and (B) min_dur=12ms. Heatmaps of AUC of the ROC curve and optimal F1 score are shown across the parameter space for patient 5, with RMS window length (RMS_win) varying on the horizontal axis and RMS threshold (nSD1) varying on the vertical axis. All values range from 0 to 1, with results closer to 1 indicating good classification of SOZ and nSOZ channels.*

Artifact rejection does not significantly impact SOZ localization

The addition of artifact rejection steps did not change the detection parameters that produced the best classification of SOZ and nSOZ channels. A representative example of localization performance before artifact rejection is shown in Fig. 4a. For this subject, the best performance, denoted by the highest optimal F1 score, occurred when the threshold was low (around nSD1 = 3-5) and across most RMS window sizes. Similar results were achieved after artifact rejection (Fig. 4b). The optimal parameter set was the same in both cases (RMS_win = 3ms, nSD1 = 4), but we note that artifact rejection improved performance for higher values of nSD1 for this patient. Across all patients, the optimal parameters were preserved after artifact rejection, with some improvement for other parameter sets.

The percent of rejected candidates varied across the parameter space (Fig. 4c, d). Near the optimal parameter set, the percent of rejected candidates by popDet ranged from 5.2 – 8% and by BkgStabaDet ranged from 6.6 – 9% for this representative example. Generally, higher percentages of detected events were rejected as artifacts when the RMS window was short and the threshold was high (top left corner of Fig. 4c, d). In contrast, the smallest percentages of rejected candidates occurred when the RMS window was long and the threshold was low (bottom right). This pattern was similar across all patients and for both artifact rejection methods. The total percentage of rejected candidates was also generally consistent across patients.

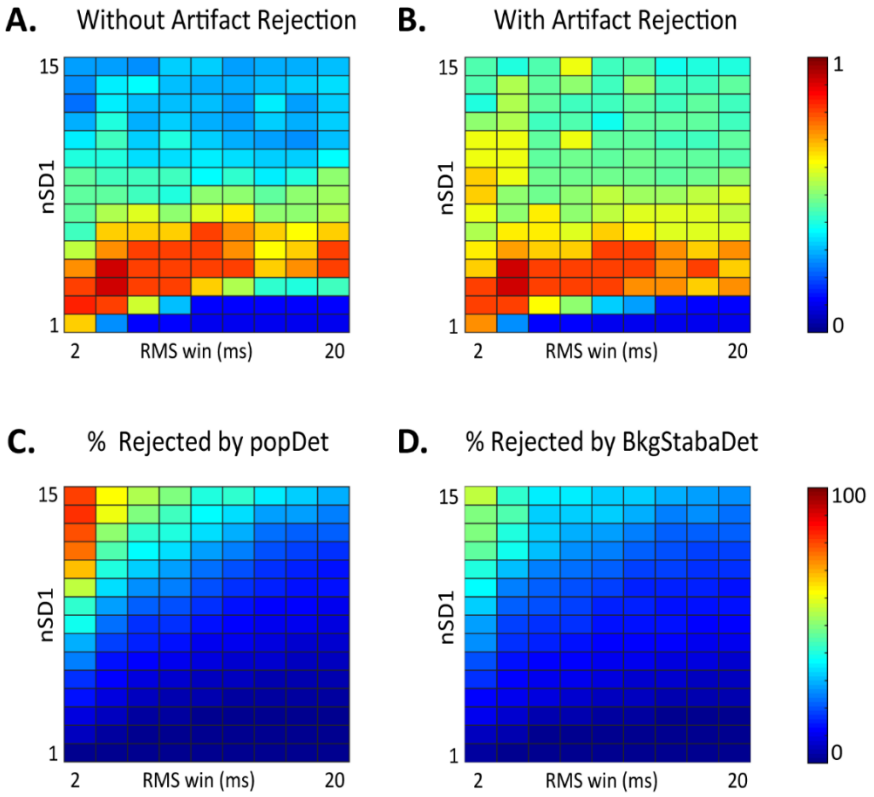

Figure 4. *Artifact rejection does not impact the optimal detection parameters. Comparison of optimal F1 scores (A) without and (B) with artifact rejection across the parameter space. Percentage of candidate events rejected by (C) popDet and (D) BkgStabaDet across the parameter space. Results from patient 5 are shown as a representative example.*

Optimal parameters are patient-specific and vary across a wide range

The optimal HFO detection parameters, which provided the most accurate classification of SOZ and nSOZ channels, varied across patients. Figure 5 displays the SOZ localization results for all twenty patients reported as optimal F1 score of the PR curve (left) and AUC of the ROC curve (middle). Similar results were obtained for the maximum AUC of the PR curve and optimal cutoff of the ROC curve (Supplementary Fig. S2). A consistent range of generally good performance was found for all patients as both the RMS window and threshold increased (indicated by the red bands stretching from the lower left corner to the upper right corner). However, within this range, patients had their own subrange of optimal

parameters. Four of the twenty patients (patients 4, 5, 7, and 17) displayed a pattern with optimal values at or near the default detection parameters. These same patients reported high optimal F1 scores and AUC values, indicating a clear distinction between channels classified as SOZ and nSOZ based on HFO rate. Based on the optimal F1 score results, four other patients (patients 2, 3, 8, and 19) had optimal performance using a higher threshold and larger RMS window than the default parameters. However, patient 8 obtained similar localization accuracy at the default parameters and the optimal parameters. In six patients (patients 4, 7, 15, 16, 17, 18), the optimal parameters were spread over a wide range that included various RMS window lengths, indicating little influence of the RMS window parameter on detection. Five patients (patients 1, 6, 14, 19, and 20) had low optimal F1 scores across the parameter space, suggesting a substantial presence of false positives. However, three of these patients (patients 6, 14, and 20) displayed favorable results based on the ROC curve, indicating that the number of true positives was also high.

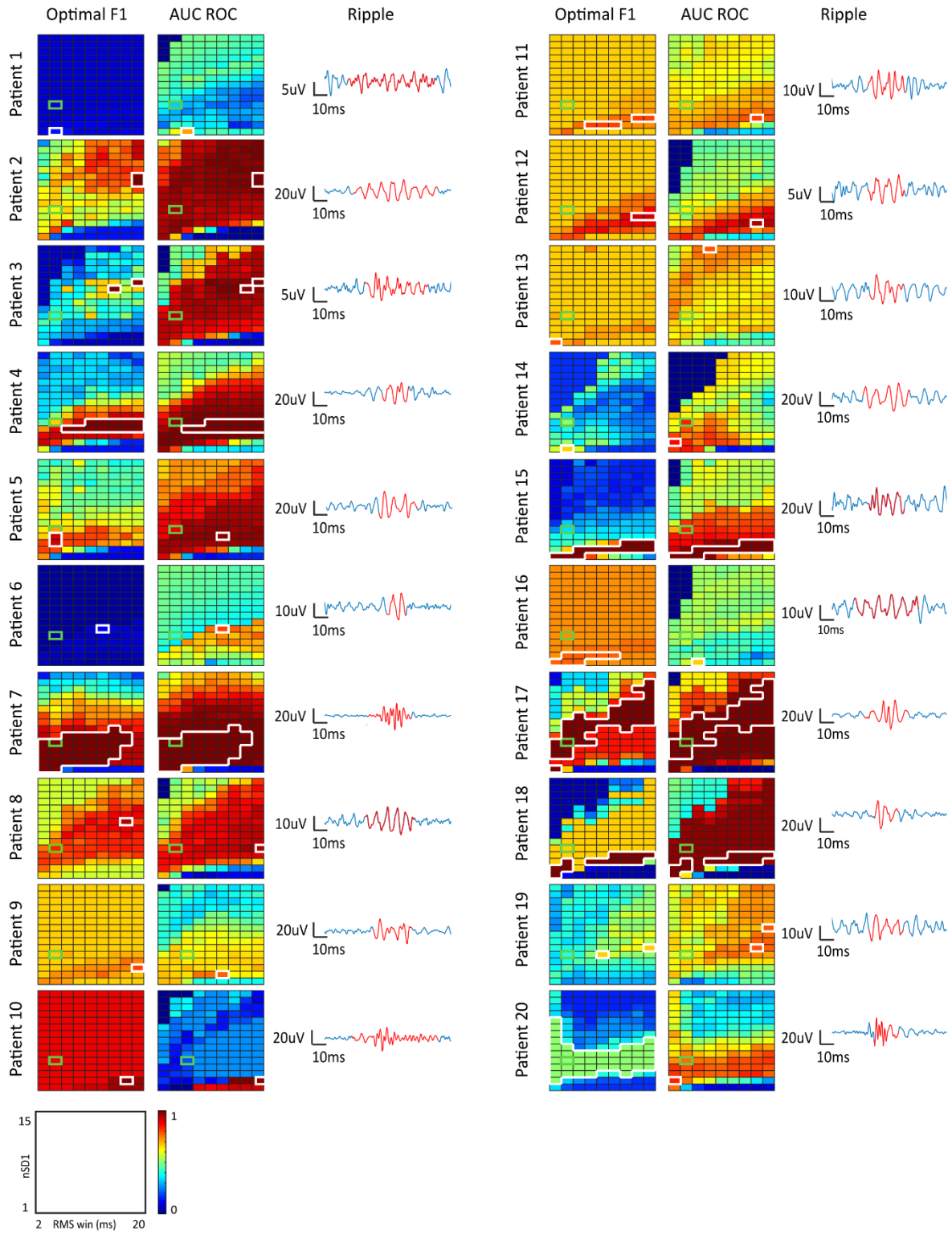

Figure 5. *Optimal HFO detection parameters are patient-specific. Optimal F1 scores (left column) and AUC values of the ROC curve (middle column) across the parameter space are shown for all patients. Results based on the default detection parameters are outlined in green. Parameter sets achieving*

optimal SOZ/nSOZ classification are outlined in white. Representative ripples detected using optimal parameters are shown in the right column.

Class imbalance affects interpretation of PR and ROC results

For all seven patients from the UCI dataset (patients 1-7), the ROC results provided a greater range of optimal detection parameters than the PR results. This can be explained by the definitions of precision and false positive rate — two distinct components of the PR and ROC curve. Precision is interpreted as a positive predictive value determined by the number of true positives relative to all predicted positives, as defined in equation 3. In patients from the UCI dataset, the number of nSOZ channels considerably outnumbers the SOZ channels; this increases the probability of marking a false positive, which increases the denominator of equation 3. Furthermore, since there are fewer SOZ channels (and therefore fewer true positives), the probability of obtaining a significant positive predictive value is low. In contrast, the false positive rate in ROC analysis is interpreted as the proportion of nSOZ channels with HFO rates above the threshold. Due to the large number of nSOZ channels (and thereby the high likelihood of having true negative channels based on HFO rate), the false positive rate can generally be kept low while the true positive rate increases, resulting in more favorable ROC results within the UCI dataset.

For example, in patient 6, good classification performance was only visible in the AUC of the ROC curve (Fig. 5). In this case, we observe that the HFO rate distribution contains a considerable number of nSOZ channels with high HFO rates (Fig. 6a). Twenty-four nSOZ channels have higher HFO rates than the SOZ channel, thereby giving a poor PR curve (Fig. 6b). However, we see a better ROC result due to the large proportion of nSOZ channels with lower rates compared the SOZ channel (Fig. 6c). Therefore, nSOZ channels with high HFO rates significantly affect the positive predictive value in PR, but they have a modest effect on ROC analysis when the proportion of nSOZ channels outweighs the SOZ channels.

In contrast to the UCI dataset, most patients from the ETH Zurich dataset (patients 8-20) had wider ranges of optimal parameters based on the PR results (Fig. 5, left column) compared to the ROC results (Fig. 5, right column). This relationship is inverted compared to the UCI dataset due to the smaller sampling of analyzed electrodes and broader interpretation of the SOZ, which was defined by the resected volume. Therefore, the proportion of SOZ channels outweighs the nSOZ channels, improving the likelihood of obtaining favorable positive predictive performance. Furthermore, due to the decreased number of electrodes, we see less variation in results across the parameter space for some ETH Zurich patients (patients 9, 10, 11, 12, 13, and 16).

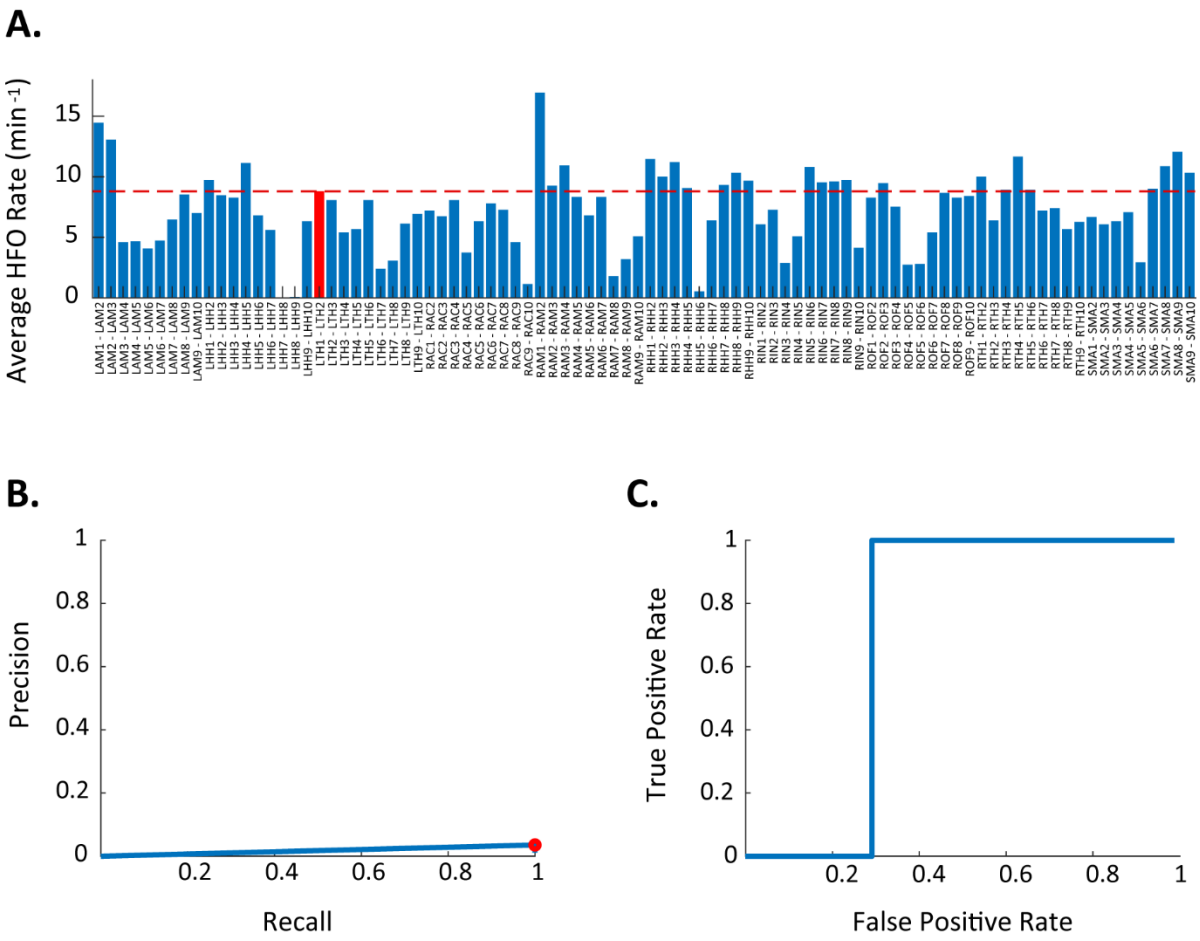

Figure 6. *Imbalanced proportion of SOZ channels and nSOZ channels alters interpretations of precision-recall and receiver-operator-characteristic results. (A) Average HFO rate for each channel in Patient 6 using an RMS threshold of three standard deviations (nSD1=3), RMS window size of 20ms (rms_win=20ms), and minimum event duration of 6ms (min_dur=6ms). (B) The resulting PR curve with*

the optimal F1 point circled in red, and (C) the ROC curve. The low number of SOZ channels (relative to the large number of nSOZ channels) negatively impacts the PR curve when the number of false positives is high, but it minimally impacts the ROC curve.

Optimizing HFO detection parameters improves SOZ localization

For each patient, we determined the optimal parameter sets based on the highest optimal F1 score and AUC of the ROC curve, then compared the results obtained from these parameters to the default detection parameters (Fig. 7). In total, seventeen of the twenty patients (85%) showed improved localization results using optimized detection parameters, while the remaining three maintained the same results. We found substantial increases in optimal F1 scores (>0.2) for eight of the twenty patients (patients 2, 3, 4, 5, 12, 15, 18, 19; Fig. 7a). Two patients (patients 7 and 17) showed no change in optimal F1 score or AUC because the optimal parameters matched the default parameters with good localization accuracy. Patient 20 also showed no change in the optimal F1 score due to consistent optimal and default parameters, however showed improvement in AUC. Six patients (patients 8, 9, 10, 11, 13, and 16) had reasonable localization results (optimal F1 score > 0.6) using default parameters, however still showed improvement in optimal F1 using optimal parameters. The remaining three patients (patients 1, 6 and 14) showed marginal growth in optimal F1 scores with optimization, but the value did not exceed 0.65. Note that improvements in ROC results carry more weight than improvements in optimal F1 scores because the optimal F1 score represents the best localization possible (at a single rate threshold), while the AUC represents the overall localization accuracy across a range of rate thresholds.

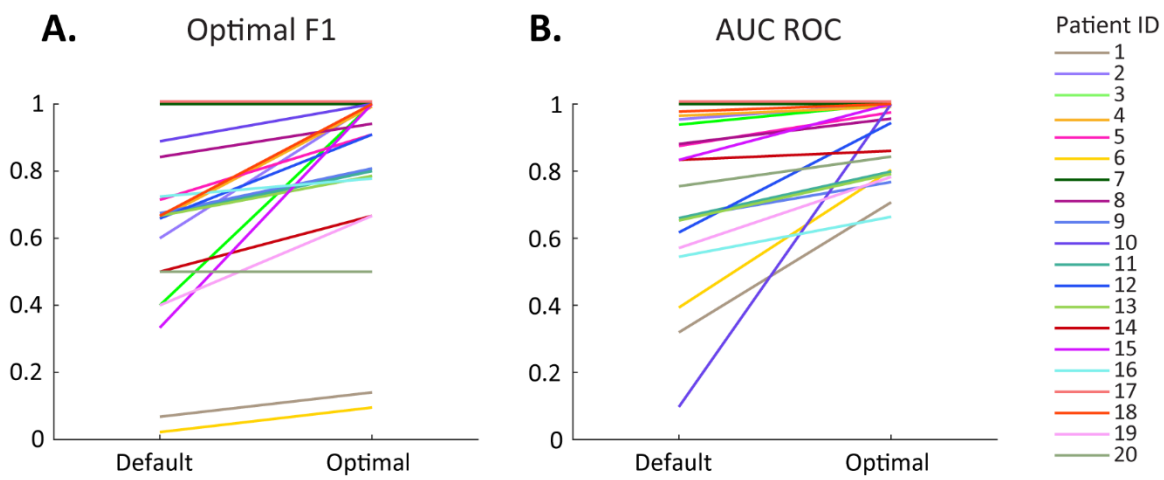

Figure 7. *The use of optimal HFO detection parameters improves precision, sensitivity, and specificity. Results for default values vs. optimal values are shown for (A) Optimal F1 scores and (B) AUC of the ROC curve for all patients.*

We assessed the number of observed true positive and false positive channels in each patient to evaluate the clinical relevance of the difference in classification accuracy using optimal versus default detection parameters (Fig. 8). The optimal parameter set and optimal rate thresholds were determined based on the highest optimal F1 score. In four patients (patients 2, 4, 9, and 19), the number of true positives increased using optimal detection parameters compared to default (Fig. 8a). For three of the four patients (patients 2, 4, and 19), the difference in marked true positives with optimal detection parameters was at least 20% of all SOZ channels, indicating a substantial improvement in SOZ localization. Only two patients (patients 12 and 13), both from the ETH Zurich dataset, had a greater number of true positives with default parameters, however the difference was only one channel. In sixteen of the twenty patients, the number of true negatives increased with optimal detection parameters, with differences ranging from +1 to +70 (Fig. 8B). This suggests that optimization of HFO detection can substantially decrease the likelihood of misidentifying nSOZ channels as SOZ channels based on HFO rate. Overall, seventeen of

the twenty patients showed improved SOZ localization with optimal parameters, while the remaining three showed results consistent with default parameters.

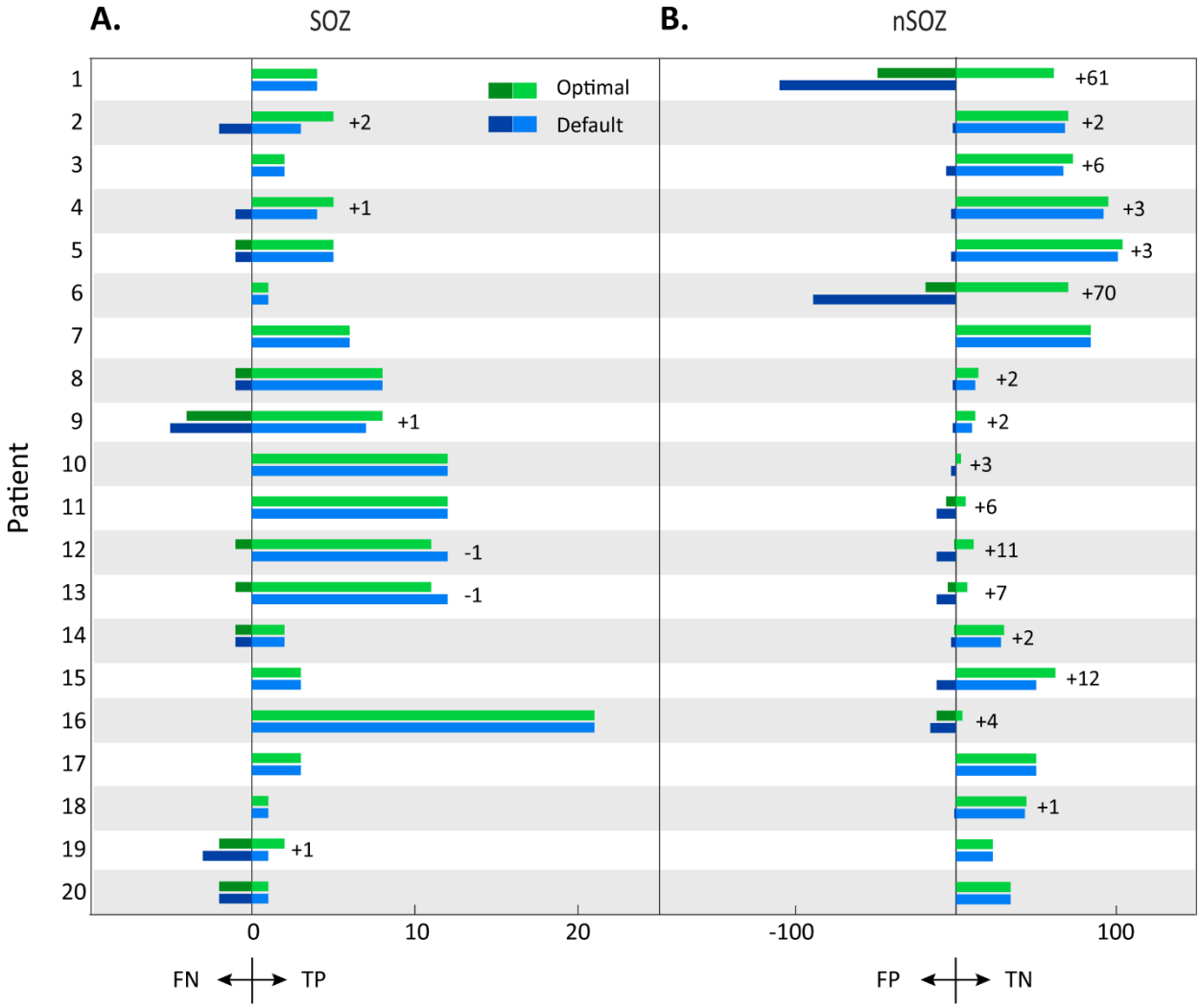

Figure 8. *The use of optimal HFO detection parameters increases the number of observed true positives in the SOZ and true negatives in the nSOZ. The number of channels for default values (blue) and optimal values (green) are shown for all patients. (A) The number of SOZ channels correctly marked as true positives (TP) are displayed as positive values, while the number of SOZ channels marked as false negatives (FN) are depicted as negative values. (B) The number of nSOZ channels correctly marked as true negatives (TN) are shown as positive values, while the nSOZ channels marked as false positives (FP) are negative. The difference in correctly classified channels using default and optimal values are listed to the right of the bar graph for each patient.*

Optimal parameters vary widely across the parameter space

For many patients, the highest classification accuracy was obtained with more than one parameter set. For each patient, we plotted all optimal parameter sets across the ranges of tested values (Fig. 9). The optimal parameters derived from the optimal F1 score (Fig. 8a) and AUC of the ROC curve (Fig. 8b) spanned the parameter space. Most patients had the same or similar optimal parameters determined from both measures; deviants from this pattern included patients 5, 8, 13, and 20. In some patients, the parameter sets spanned the entire range of RMS window sizes, but with different values of the amplitude threshold (nSD1).

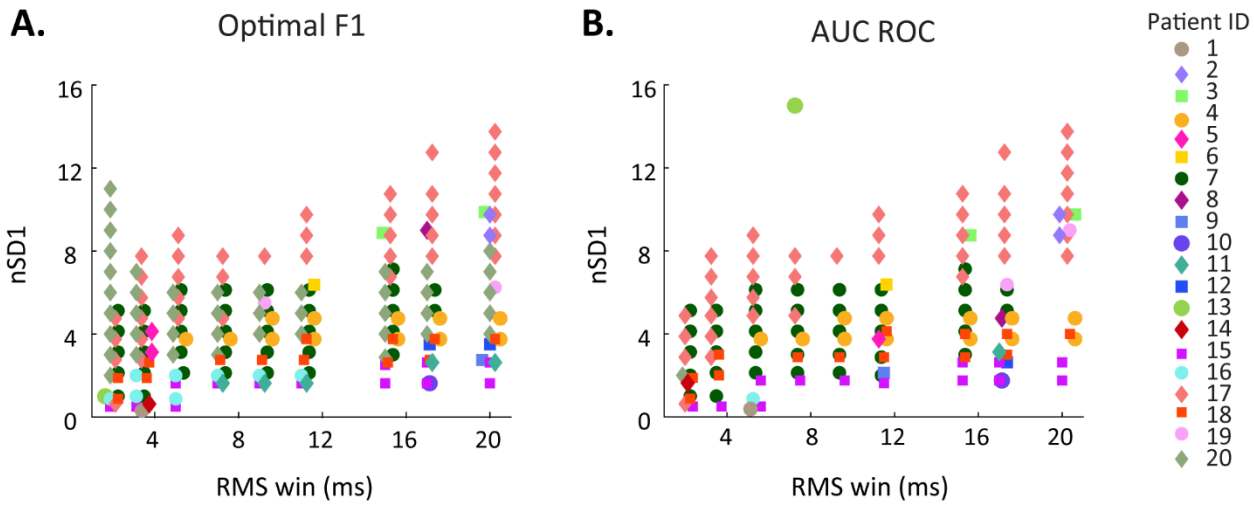

Figure 9. *Optimal HFO detection parameters based on (A) optimal F1 score and (B) AUC of the ROC curve for all patients.*

Discussion

Summary of findings

This study assessed SOZ localization accuracy over a wide range of HFO detection parameters to measure the impact of parameter optimization in two patient cohorts. In both patient populations, we found that the range of parameters for optimal classification of SOZ/nSOZ electrodes was patient-specific

and spanned a wider range of values than those used in most prior studies. The parameters with the biggest effect on SOZ localization accuracy were the RMS window length and the amplitude thresholds; in contrast, artifact rejection had minimal impact. Additionally, detection using optimal parameters led to improved localization results compared to the standard parameters established in the original publication. This suggests that proper selection of automatic detection parameters can increase the power of HFOs as a biomarker of the SOZ, and future efforts should be directed to development of patient-specific optimization procedures.

Influence of class imbalance on interpretation of results

In this study, the class imbalance (number of SOZ channels relative to nSOZ channels) affected the interpretation of the results for each patient. The number, type, and placement of electrodes varied per patient based on clinical indication, resulting in inconsistent sample sizes. Furthermore, the localized SOZ was specific to each patient, leading to variable numbers of SOZ channels and nSOZ channels. Because of this, we characterized the classification performance using both the ROC and PR curves, as they are complementary measures. The ROC curve provides valuable information on the classification sensitivity for each parameter set, and it has been widely used to characterize classification performance (Zelmann et al. 2012; Charupanit and Lopour 2017; Roehri et al. 2018). In the UCI dataset, characterized by larger proportions of nSOZ channels for all patients, we saw smaller variations in AUC ROC results across the parameter space. This was because the small proportion of SOZ channels led to true positive rates that varied only marginally as the rate threshold was varied. In contrast, the Precision-Recall curves provided valuable information on the positive predictive value (PPV) of the classification, and this method is considered to be appropriate for analysis in imbalanced datasets (Saito and Rehmsmeier 2015). Because the PPV is indicative of the proportion of true positives relative to the predicted positives, this metric varies more significantly than the true positive rate (which is used in ROC analysis). Furthermore, the PPV provides key information on the presence of false positives, which occur more frequently in the UCI

dataset than false negatives due to the small proportion of SOZ channels. As a demonstration of this, we observed more localized optimal parameter ranges for the optimal F1 scores than the AUC for all UCI patients in Fig. 5.

The patterns described here for both ROC and Precision-Recall curves were also observed in the ETH Zurich dataset, albeit reversed because the proportion of SOZ channels was greater. Because we cannot compare classification accuracy between the UCI dataset and ETH Zurich dataset directly due to the variables described, we only conclude that the patient's optimal parameters differ, and we cannot make comparisons on the performance of HFO rate as a biomarker across the patient populations. In summary, the dissimilarities in electrode sampling led to different ROC and PR outcomes, and for some patients, localization was deemed poor based on these results.

Characteristics of resulting HFO detections

Detecting HFOs over a wide range of parameters led to substantial differences in the number of HFOs detected. For parameter sets with low thresholds and small RMS windows, we detected more than 1,000 HFOs per channel over 15 minutes of data on average for all patients. These detections were likely a mix of true HFOs and false positive detections; however, in some cases, the resulting distribution of average detection rates across channels yielded favorable localization results when a rate threshold was applied. In the opposite corner of the parameter space, parameter sets with high thresholds and large RMS windows contained very few detections. These events needed to have inordinately high amplitude to meet the threshold and minimum event duration criteria, especially because the amplitude was damped by the use of a large RMS window. We detected very few of these events, as low as 0-3 detections across all channels, which likely led to the unreliable localization results when using these extreme parameters. However, the best localization results for patient 2 occurred for such parameter sets (nSD1 = 9-10,

RMS_win = 20 ms). This is consistent with previous findings that demonstrate amplitude as an important metric in HFO analysis (Matsumoto et al. 2013; Malinowska et al. 2015; Charupanit et al. 2020).

Influence of underlying pathologies

A subset of patients did not achieve accurate SOZ localizations for any parameter set, and the presence of secondary pathologies or specific epilepsy disorders is one possible explanation for this. In the UCI dataset, MRI results of patients 1, 2, 3, and 6 revealed lesional or tissue abnormalities consisting of hippocampal and temporal sclerosis, cortical dysplasia of the prefrontal cortex, and imaging abnormalities in the frontal cortex. The presence of these secondary pathologies may have influenced the HFO rates detected in these regions, due to various types of neuronal derangements in abnormal brain tissue (Ferrari-Marinho et al. 2015). Regarding the influence of epilepsy disorder on HFO rate in the SOZ, previous studies have found distinctions between patients with temporal and extratemporal epilepsy. For example, Guragain et al. (2018) and Haegelen et al. (2013) examined the spatial mapping of HFOs and found that patients with extratemporal epilepsy disorders did not contain significantly elevated HFOs rates in the SOZ compared to the nSOZ. In contrast, patients with mesial temporal lobe epilepsy showed significantly elevated HFO rates in the SOZ, suggesting that HFOs may be a specific marker for patients with mesial temporal lobe epilepsies (Bragin et al. 1999; Staba et al. 2004; Worrell et al. 2008). Similar distinctions were found between patients with neocortical epilepsies and mesial temporal lobe epilepsies, where patients with neocortical epilepsies did not exhibit HFOs in epileptic structures or healthy regions (Crépon et al. 2010). However, HFOs were recorded in the SOZ of all patients with mesial temporal lobe epilepsy (Crépon et al. 2010). Of the UCI patients included in this study, patient 1 was diagnosed with frontal lobe epilepsy, which may explain the suboptimal SOZ localization results across all parameter sets. Similarly, patients 14-20 from the ETH Zurich dataset were diagnosed with extratemporal epilepsy and underwent lesionectomy, which may have influenced localization because different lesion types have various levels of intrinsic epileptogenicity and may contribute dissimilarly to epileptogenic networks

(Jacobs et al. 2009). In summary, underlying pathologies may play a role in the ability to accurately localize the SOZ based on findings within our cohort; however, additional patients should be studied to make robust conclusions.

Limitations and future work

There are several limitations to our work. Our study demonstrates that patient-specific optimization can significantly improve SOZ localization using HFOs; however, two important questions remain unanswered. First, how could such optimization be implemented in clinical practice? Our analysis was retrospective, and we reported the best possible localization results assuming that the optimal detection parameters were chosen; however, in clinical practice, optimization would need to be performed on a reserved subset of patient data and without prior knowledge of the SOZ. Without knowledge of the SOZ, the detector could be optimized to match visually detected HFOs, but this approach may not reliably correlate to optimal surgical outcome. Thus, future work should address methods for implementation of per-patient optimization in clinical settings. Second, is the improvement in SOZ localization due to HFO detection parameter optimization clinically meaningful? For example, if the AUC increases from 0.80 to 0.85 due to parameter optimization, would this change the patient's treatment or outcome? We have estimated the improvement due to optimization by quantifying the differences in observed true positive and false positive channels; however, the long-term impact on surgical outcome for each patient cannot be predicted. Future work should aim to address the question of what constitutes clinically meaningful improvement.

Another limitation was the relatively small cohort size. However, our results were consistent across two independent datasets, with each dataset demonstrating patient-specific variability in optimal parameters. This was the main goal of our study. Also, the ETH Zurich dataset delineated the SOZ based on resected volume, while the UCI dataset used ictal EEG analysis, and both datasets contained varying class

imbalances that affected our interpretation of the SOZ localization results. These differences restricted our ability to make more definitive conclusions regarding SOZ localization. The resected volume is typically a larger region of the brain that encompasses the EEG-defined SOZ. Therefore, the SOZ was more loosely defined for the ETH Zurich dataset, which also had varying numbers of recording channels, and this likely affected ROC and PR results.

Regarding automatic HFO detection, we aimed to analyze artifact-free intracranial EEG data during sleep. However, concurrent scalp EEG was not available for the UCI dataset, and the data were therefore not sleep staged. Previous studies have shown that HFO activity varies across wakefulness and sleep and for specific sleep stages (Clemens et al. 2003; Staba et al. 2004; Bagshaw et al. 2009). Therefore, ensuring that all data were recorded during the same sleep stage may provide more accurate results. Another limitation in our study was the lack of optimization of our artifact rejection methods. Although Gliske et al. (2016) performed an optimization procedure to determine the rejection threshold of the popDet, one set of parameters does not necessarily work equally well for all patients, as we have shown here. Furthermore, Gliske et al. (2016) tested the threshold ranging from 5 to 15 standard deviations; however, in some of our patients, we found that the popDet performed better using a lower threshold. Ideally, to improve localization results, visual validation on a reserved subset of data should be used to optimize parameters for artifact rejection.

Conclusion

This study examined the impact of optimization of automatic HFO detection parameters on SOZ localization in medically refractory epilepsy patients. All patients achieved seizure freedom following resective surgery, and the majority of patients exhibited elevated HFO rates in the SOZ, which led to favorable localization results. However, only 15% of these patients achieved their maximum localization accuracy using conventional detection parameters, highlighting the significance of patient variability and the importance of tuning automatic HFO detectors. Future studies should propose patient-specific

optimization techniques for the clinical setting and examine the characteristics of pathological HFOs that provide optimal classification of SOZ and nSOZ channels.

Conflict of Interest Statement

None of the authors have potential conflicts of interest to be disclosed.

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Supplementary Figure 1

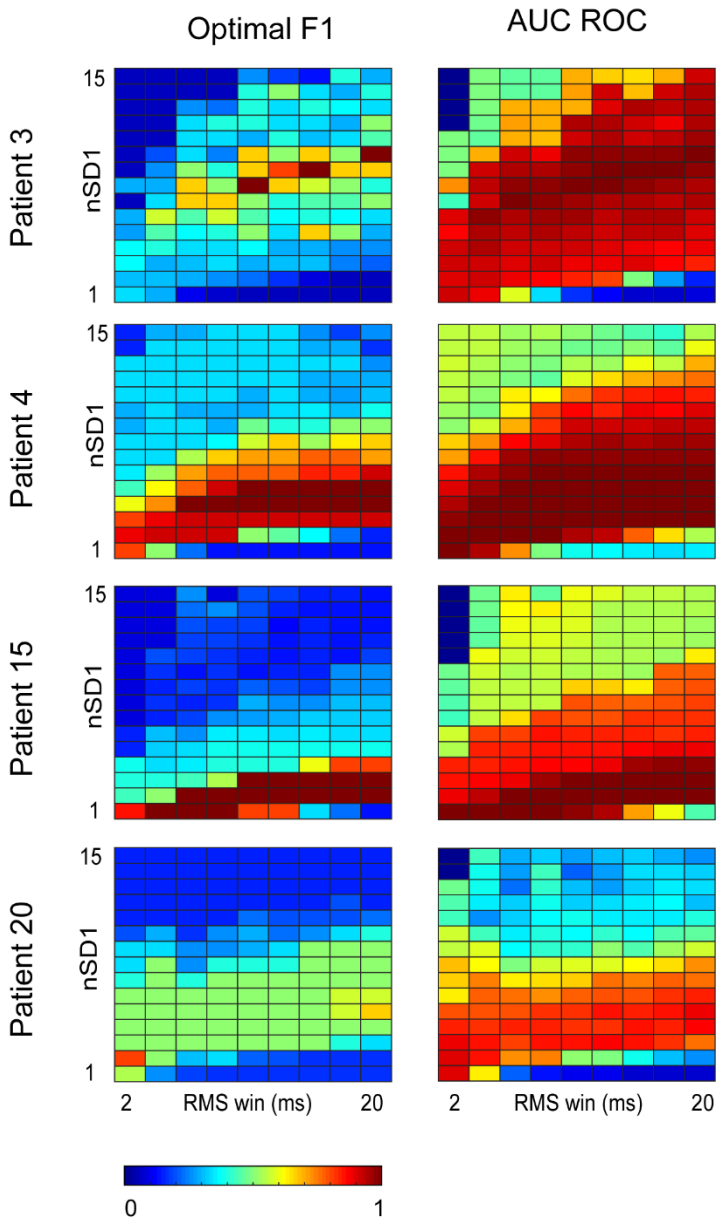

Figure S1. *Representative heatmaps of optimal F1 and AUC of the ROC curve using minimum event duration of 12ms (min_dur=12ms) are shown across the parameter space for patients 3 and 4 from the UCI dataset and patients 15 and 20 from the ETH Zurich dataset. This can be compared to the results in Figure 5 which used min_dur=6ms.*

Supplementary Figure 2

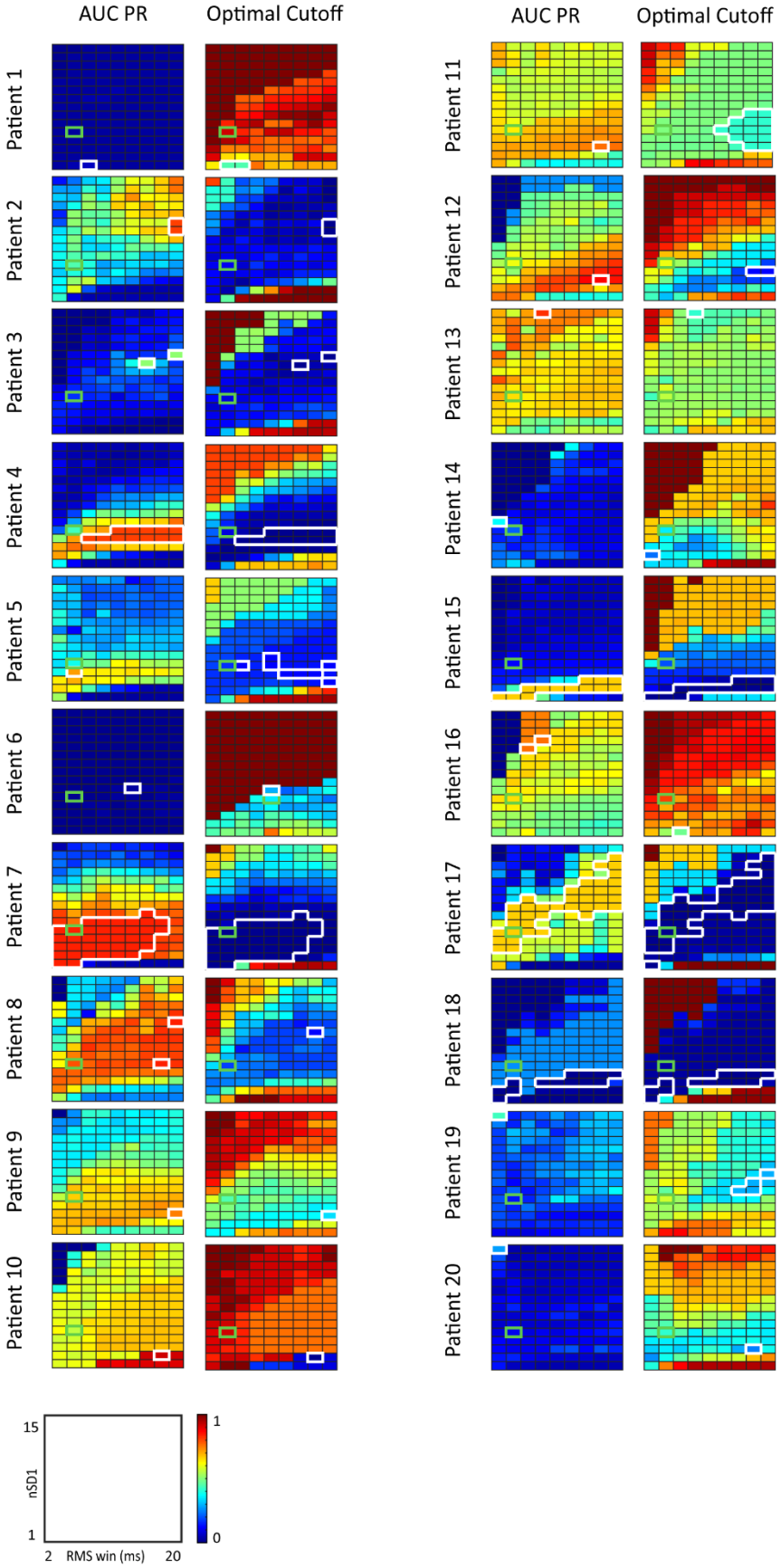

Figure S1. *AUC of the PR curve (left column) and optimal cutoff distance for the ROC curve (right column) across the parameter space are shown for all patients. Results based on the default parameters are outlined in green. Parameter sets achieving optimal SOZ/nSOZ classification are outlined in white.*