의 학 박 사 학 위 논 문

데이터 마이닝에 기반한 신피질 뇌전증에서 예후와 관련된 두개강 내 발작간기 활동의 선택

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박 성 철

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Data-mining for selection of interictal electrocorticographic activities based on seizure outcome in neocortical epilepsy

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Abstract

Data-mining for selection of interictal electrocorticographic activities based on seizure outcome in neocortical epilepsy

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Introduction: We introduce a new data-mining method to select interictal pathologic activities based on the outcome of resective epilepsy surgery defined as the presence/absence of seizures in neocortical epilepsy (NE).

Methods: We analyzed electrocorticographies from 39 patients with medically intractable NE. We separately analyzed 37 frequency-bins from 0.9 to 600 Hz to select the bands related to the seizure outcome. An automatic detector using amplitude-duration-number thresholds was used. The two different interictal electrocorticography datasets containing epileptiform activities were selected. In the first training dataset, the automatic detector was optimized to best differentiate the seizure-free group from the not-seizure-free-group based on the ranks of resection percentages of the activities detected using a genetic algorithm. We optimized in a patient group with 20 patients and validated optimized threshold in a different patient group with 19 patients to evaluate stability of results in a different patient group. Significant reproducibility was determined from expected numbers of significant results from the binomial distribution. The differences in the resection percentage of the detected activities between the seizure outcome groups (Dif-R) in the validation dataset were measured.

Results: There were 16 seizure-free (41%) of 39 patients. The mean follow-up duration was 21 ± 11 months (13 to 44 months). In the validation dataset from the different 19 patient group,

delta in 2.0 – 2.3 Hz were significantly reproducible. Low-frequency activities (LFAs) between 4.9 – 43 Hz including theta, alpha, beta and low-gamma were significantly reproducible. High-gamma in 62 and 75 Hz and high-frequency activities (HFAs) in 108 and 322 Hz were reproducibly related to seizure outcome. Dif-Rs in the different patient group was about mean 10 – 20 % in reproducible frequency-bins. In LFAs, the resection of detected activities were positively related with better seizure outcome as intended. However, high-gamma activities are paradoxically negatively related with seizure outcome.

Conclusion: Using the presented method, in a different interictal segment validation, we achieved Dif-Rs that were higher than the best manual and automatic HFA detections described in the literature using only training dataset (17 to 27 %). In a different patient group validation, our results, 10 – 20 % Dif-Rs were comparable to literature analyzing only training dataset. A new method selecting pathologic activities based on seizure outcome can be potentially useful finding pathologic activities to be resected.

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Keywords : Effect-sizes; High-frequency activity; Low-frequency activity; Optimization; Reproducibility; Seizure outcome

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1 Introduction

Epilepsy epidemiology and economic burden

The prevalence of epilepsy in Korea is 2.4/1,000 – 3.52/1,000 and there were 171,806 patients in a survey performed by Korean epilepsy society (1). Medical cost for epilepsy occupies 0.46% of total national medical costs. The direct medical cost was 232 billion won (2). In Germany, medical cost per person in tertiary referral hospital was 12,000 dollar (3). Thus, the medical burden of epilepsy is substantial and reducing it is important.

Medically intractable epilepsy and epilepsy surgery

The first-line treatment for epilepsy is antiepileptic medications (4). However, 30 % of epilepsy patients do not become seizure-free with medication (4). Although, various antiepileptic medications have been developed for decades, about 1/3 of epilepsy patients are still refractory (5). The medical refractoriness is defined when the patient still suffer seizure in spite of the proper use of two kinds of antiepileptic medications (6). Medical refractoriness of epilepsy is a severe problem which can cause sudden death (SUDEP) and cognitive disturbances (7). For these patients, non-medical treatment modalities are required. Thus, these patients are indicated for resective epilepsy surgery to control seizure when it is possible.

The resective epilepsy surgery is to resect some region of brain to control seizures (8). In this type of epilepsy surgery, the epileptogenic zone is the area which need to be resected to achieve seizure-free outcome (8). The possibility of resective epilepsy surgery depends on the type of epilepsy. Epilepsy surgery is known to be highly effective with about 70 – 90 % seizure free rate and cost effective for a few epilepsy types including especially anterior temporal lobe epilepsy (9, 10). The resective epilepsy surgery can achieve good outcome up to 70 – 80 % in well selected and correctly guided with ECoG (11).

In neocortical epilepsy, medically intractable epilepsy frequently has a specific cause which can

be localized, for example, cortical dysplasia (12) or epileptogenic tumors (12). Some inflammatory and intracellular signaling pathways causing epilepsy may be identical between cortical dysplasia and glioneuronal tumors (12). However, in many cases of neocortical epilepsy, potential pathologies causing epilepsy are unclear (13). In addition, epilepsy surgery outcome is worse in these cases with no lesions. Thus, in these non-lesional epilepsy patients, preoperative evaluations to find out unseen epileptogenic zone is important. Among preoperative evaluations, ECoG has the highest temporal and spatial resolution than the other noninvasive studies (14). Thus, the purpose of preoperative evaluations for epilepsy surgery and electroencephalographic (EEG) and electrocorticographic (ECoG) evaluations for epilepsy surgery is to find the epileptogenic zone from pathologic ECoG activities (14, 15). After evaluations, when the epileptogenesis seems to occur from local area, resective surgery can be undertaken. However, the extent of the epileptogenic zone is hard to know in many epilepsy patients, especially nonlesional neocortical epilepsy. Thus, epilepsy surgery may fail in considerable percentage of patients and further operation may be required (16).

Physical model of epileptogenesis and unpredictable seizure outcome

The concept of epileptogenic zone is rather vague and not very helpful or practical for epilepsy surgery. Because the epileptogenic zone is defined based on postoperative outcome of epilepsy surgery, the epileptogenic zone cannot be known before the surgery is undertaken. In addition, the concept of the epileptogenic zone does not have information about the surgical target which should be resected. Furthermore, the concept of the epileptogenic zone imply that the area which should be resected is localized and determined. However, portions of epileptogenic network which should be resected may be variable and may not focal. For example, callostomy does not resect any volume or zone in brain. However, some patients can become seizure free after callosotomy (17). This finding shows that connectivity change without volume resection can achieve seizure free outcome. Therefore, a different non-localized epilepsy model is required.

The concept of epileptogenic zone suppose rather simple and linear relationship between the epileptogenic zone and seizure outcome (8). In the concept of the epileptogenic zone, the complete resection of the epileptogenic zone is related with seizure free outcome and partial resection is not completely seizure-free outcome (8). However, in real ECoG data, the relationship between the seizure outcome, ECoG and seizure outcome is not simply linear. Wide resection of seizure onset zones may not reduce seizures at all or may improve seizures. The relationship between seizure onset zone resection and seizure outcome may be poor especially in neocortical epilepsy (13). Thus, current linear concept of the epileptogenic zone is far from real epileptogenesis from nonlinear (18, 19) and network interaction dynamics (20). Therefore, seizure outcome cannot be explained with simple linear expectations. To explain and predict the currently not understood phenomenon of seizure outcome after epilepsy surgery based on ECoG, new model considering both nonlinearity and network dynamic interactions (20, 21) which result in nonlinearity and bistability. seizures are not arising from a point as a linear process. Instead, dynamic nonlinear state changes may be a more exact feature of seizure generation (20, 21). The epileptogenesis model which can overcome limitations of localized model should consider dynamic interactions among brain regions which may occur at alpha or theta bands (20). In this study, we also included low-frequency activities (LFAs) and the results in LFAs may be related to more widespread network-related pathology.

Low and high-frequency electrocorticographic activity based epilepsy surgery planning

Since the advent of EEG, only LFAs were used for clinical purposes for about a hundred years. Before the discovery of high-frequency activities (HFAs), the band to be used clinically was usually < 75 – 80 Hz in EEG and ECoG (22). This band is referred as LFAs in comparison to HFAs in recent literature (22). LFAs are suggested to be related with seizure outcome in studies using conventional EEG (15, 23). The LFAs, especially spikes were suggested to be worse in relation to seizure outcome in a few HFA studies (24). However, epilepsy surgery outcome is not perfect especially in neocortical epilepsy (13). New methods to improve seizure outcome is

being sought. One of new method being investigated was high-frequency analysis in epilepsy (25).

However, LFAs and HFAs have not been properly compared previously. Instead, there are several studies significant relationship between seizure outcome and LFAs (15, 23). Furthermore, the significance and reproducibility of HFAs are still unclear. In a recent study, low inter-rater reliability of HFAs were reported (26). Thus, to elucidate the significance of both HFAs and LFAs, we performed data-mining using signal processing and machine learning methods.

In addition, there is still no objective method to use information contained in ECoG for epilepsy surgery planning. Thus, reproducibility of the current ECoG analysis method is not established and may be limited. In addition, the current visual analysis of ECoG may be suboptimal for best seizure outcome. Thus, a reproducible and verified method better optimized for the currently available dataset would be required.

Definitions of high-frequency activities (HFAs) and high-frequency oscillations (HFOs) and exceptions

In early studies about pathologic signals in high-frequency band, the term high-frequency activities (HFAs) were commonly used (27, 28). The term HFAs are also previously and currently (29) used in multiple literature as a wide meaning including fast activities in gamma band.

Also in some recent literature, the term HFAs are used as a wide meaning including HFOs such as ripples and fast ripples (30). HFAs are frequently used terminology to designate pathologic high-frequency band signals before the advent of the concept of HFOs. However, HFAs may be used to designate especially continuous activities in some studies as explained next.

The term high-frequency oscillations, (HFOs) is a narrower and more specific concept than HFAs. There are two kinds of HFOs, ripples (100 – 200 Hz) and fast ripples (250 – 500 Hz) (31).

High-frequency signals outside of these bands are sometimes referred as HFAs. HFOs are first observed in hippocampus (31). “Oscillation” is in definition, a repetitive or rhythmic activity. Oscillation is an inherent property of neural network and cells (32). As the term “oscillation” means, HFOs should have at least four repetitive rhythms, oscillations in definition in most HFO studies (24, 25, 33).

Some neural signals in high-frequency band may not satisfy this criterion of oscillation. In general, there can be two cases of HFAs which are not HFOs. One is too short. The other is too long. These are explained in following paragraphs. Some HFAs with short duration may be “false ripples” from band-pass filtered sharp transients (34, 35). Therefore, a criterion for HFO detection was consecutive oscillatory waveforms in unfiltered waveforms in most studies (24). However, some association with pathologic LFAs may be present for pathologic HFAs (36).

HFOs are usually discrete short-duration activities with oscillatory waveforms. However, high-frequency signals may have much longer duration in some cases (37, 38). More recently, the term HFA was used to indicate continuous or semi-continuous especially hippocampal pathologic activity in a study (37, 38). This type of HFA was also most commonly found in hippocampus (37). This terminology is a special use of the term “HFAs” in a narrow definition. This HFAs in narrow meaning was mainly used in a recent two studies from the research group led by Jean Gotman (37, 38). This pattern may be related to hippocampus and occipital lobes as a type of physiologic activity and may not related to seizure onset zones (38). This type of HFA is more specially referred as “continuous HFAs” (38).

Relationships between HFOs and LFAs

An important previously suggested characteristic of HFOs is independence from pathologic lower frequency activities (LFAs) (24). In a recent study investing pathologic gamma activities phase locked to lower frequency activities, the term HFAs (29) were used. However, it is controversial that whether independence from the LFAs is important. For example, ripples associated with pathologic LFAs were suggested to be pathologic in a study (36). In a different study, ripples in flat background were suggested to be pathologic and ripples with oscillatory

background was suggested not to be pathologic (39).

HFO Recording techniques and electrodes

HFO was first discovered in microelectrode recordings in hippocampus (31). HFO recorded in microelectrode was suggested to have better signal quality (40). Especially, fast-ripple was predominantly recorded in microelectrdes (40). In contrast, macroelectrdoes primarily recorded ripples in lower frequency range (40). Thus, studies investigating fast ripples may be limited when macroelectrode is used.

HFAs are also suggested to be recorded in scalp electroencephalography (EEG) and magnetoencephalography (MEG). However, muscle artifacts are also found in high-frequency band and can interfere the analysis (41). Signal amplitudes of intracranial HFAs in scalp EEG may be low. However, some studies suggest that scalp HFOs are still identifiable (42, 43).

In early period of HFO research, it was controversial that HFO could be detected in macroelectrode (40). Recording quality in macroelectrode was concerned in early studies and can still influence the analysis result (40). Significance of subdural macroelectrode HFO was suggested in a previous study (44). We used electrocorticography which has better signal quality than noninvasive recordings (33, 45-47). Therefore, microelectrode or microelectrode array recording with higher spatial resolution, which may better detect HFAs or multi-unit activities, may potentially show different results (40, 48).

Adequate interictal segment to investigate: durations and sleep cycles

In some studies, the duration of the interictal HFA analysis period was about five minutes (25, 33). However, a recent intraoperative study suggested that one minute segments also contains significant information about HFAs (49). We presumed that one and three minute interictal periods are enough for the reproducible analysis considering very high-reproducibility in LFAs. However, a longer five minute segment potentially had advantage in analyzing LFAs with

longer duration activities. In addition, longer interictal periods may be beneficial for better regularization and data augmentation. For better regularization and statistical power, we used data augmentation technique selecting multiple interictal segments in a patient.

In most studies, stage III or IV sleep segment is recommended for the analysis (24, 25). This segment can be free from muscle and motion artifacts. In addition, sleep may promote appearance of pathologic HFOs similarly to spikes (24, 25). HFOs among sleep stages were not significantly different when awake and REM sleep stages are excluded (24, 25).

Physiologic and pathologic HFOs and relationships to seizure outcome

Physiologic HFOs are also known especially in ripple band in hippocampus (50). The underlying mechanism is suggested as summed inhibitory post-synaptic potentials in pyramidal cells from high-frequency barrage of interneurons (50). In addition, neocortical physiologic HFOs are also well known especially in functional cortices (51). Sensory-evoked HFOs can occur in neocortices in 200 – 600 Hz (51). In contrast, pathologic HFOs are associated with hippocampal sclerosis (31) or other neocortical pathologies including cortical dysplasia. The amplitude threshold, about 5 standard deviations are an approximate distinction between physiologic HFOs and pathologic HFOs (52). However, there is considerable overlap between physiologic HFOs and pathologic HFOs (51, 52).

Previous studies about electrocorticographic (ECoG) activities, including high-frequency activities (HFAs) found that the relationship between ECoG activities and seizure outcomes is variable (25, 33, 45, 49, 53, 54). Specifically, gamma and ripples (RPs) were inconsistent regarding its relation to seizure outcome (25, 33, 45, 49, 53, 54). This inconsistent reproducibility is most likely because physiologic and pathologic activities are intermixed, especially in the gamma-RP band (8, 22, 24, 33, 45, 50, 54-59). Therefore, separating pathologic and physiologic activities is crucial in analyzing ECoG to find activities reproducibly related to seizure outcome. Therefore, various methods, including fast ripple (FR) to RP ratio indices, phase-locking to epileptiform activities, and machine learning algorithms, were used to discriminate pathologic and physiologic HFAs (36, 52, 57, 59, 60). However, complete source

separation of pathologic and physiologic activities may be difficult in macroelectrode ECoG (61, 62).

Generation mechanisms of pathologic HFOs and low HFO amplitudes

HFAs in NE are probably arose from more asynchronous out-of-phase neural firings (63) resulting in wide reproducible bandwidths than HFAs in mesial temporal lobe epilepsy from more synchronous (64) in-phase neural firings resulting in narrow reproducible bandwidth. Greater asynchrony of HFAs in NE may result in greater inter-cancellation between HFAs in turn causing difficulty of reliable detections in macroelectrodes (63). In addition, higher frequency band of neural oscillation has inherently lower amplitudes decreasing in log-scale (47). Because of low-amplitudes of HFAs, we speculate that HFAs are more difficult to differentiate reproducibly from baseline noise and physiologic activities (52, 65) than LFAs. Thus, detections of HFAs probably became inevitably more specific (43) and only high effect-size HFAs can be reproducibly analyzed in very focal areas in a subgroup of patients when macroelectrode recording is used. As a result, the reproducibility, the inter-rater reliability (26) and clinical utility may be lower than initially expected in early studies. This hypothesis is supported from a previous report that a universal detection threshold is almost nonexistent for HFAs in NE (46).

Manual automatic detection methods for pathologic HFAs and HFOs

In a recent study, inter-rater reliability of HFO detections was suggested to be low (26). This finding suggests that manual analysis which are not extensively verified is not clinically useful. However, most previous automatic analysis algorithms for ECoG high-frequency activities (HFAs) and medical data were trained based on manual visual annotation results by human experts (66, 67). By this method, an automatic analysis cannot outperform human observer and eventually analysis result will be optimized to be similar to human observer. Furthermore, it is unclear that manual classification by a human observer is correct and can be considered as a

gold standard especially in HFAs analysis, a relatively new biomarker for which human experts are not also trained enough. However, if an automatic algorithm is trained by reinforcement learning based on outcome, it can potentially outperform human expert and the other automatic algorithms which are not trained based on outcome.

Thus, a different optimization method for pathologic HFA detections is clearly needed. Therefore, more objective and automatic large-scale data-mining paradigm was suggested suggesting potential improvements of ECoG HFA analysis techniques (68, 69). For HFA and ECoG data-mining, we introduce a new optimization method using seizure outcome in this study. The outcome of decisions, for example, the victory or defeat in a game is an effective training feedback for machine learning (70). This training method has led to superhuman performance in some applications. For example, an artificial intelligence program outperformed professional human Go players after the reinforcement training based on the outcome of games (70). We hypothesized that the same reinforcement learning can be applied for the detection of pathological activity in epilepsy surgery. In epilepsy surgery, victory is defined as a seizure-free outcome for the patient, and defeat as a not-seizure-free outcome. If an automatic detector is trained by the reinforcement machine learning based on the outcome, it can potentially outperform human experts and previous automatic algorithms that are not trained based on outcome. We aimed to evaluate whether this method outperforms previous manual and automatic detections.

Epilepsy types and HFOs

HFOs were first reported in mesial temporal lobe epilepsy (31). However, HFOs in neocortical epilepsy was also reported in multiple studies (36, 46, 69, 71, 72). However, HFOs in neocortical epilepsy may be less conspicuous and harder to discern from physiologic activities (51). Especially fast ripples may be more important in mesial temporal lobe epilepsy (57, 63) and gamma and high-gamma band more important in neocortical epilepsy (53).

We investigated homogeneous epilepsy subtype, NE, excluding mesial temporal lobe epilepsy. We used ECoG from a series of 39 neocortical epilepsy (NE) patients that was much larger than

the ones described in previous NE HFA studies including 11 (46) or 9 NE patients (33). The thresholds in these previous studies that separately analyzed NE groups were not extensively optimized using machine learning. Instead, manual visual marking methods (33, 46) and individualized thresholds (46) were used to detect HFAs.

Investigating both LFAs and HFAs based on seizure outcome for proper comparisons

In some studies, the presence of epileptiform activities was suggested to be important to determine the adequate interictal period for the HFA analysis (36, 50, 73-76). In addition, LFAs may have comparable efficacy to HFAs (76). Other recent studies suggested that a combined analysis of LFAs and HFAs could elucidate epileptogenic activities and networks (36, 77). Therefore, we analyzed broadband ECoG, including both HFAs and LFAs, in the interictal period with abundant epileptiform activities.

In addition, we suggest that LFAs and HFAs can be properly compared by the reinforcement learning used for both band. HFA and LFA analysis results including sensitivities and specificities may vary according to difference in methodological details and detection thresholds (78). Most previous studies about high-frequency activities (HFAs) suggested that HFAs are more important than low-frequency activities (LFAs) (25, 79). However, these studies compared HFAs only with spikes among epileptiform LFAs. In addition, these studies suggested that patients with a good outcome do not have larger proportions of spike-generating areas or seizure onset zones removed by epilepsy surgery than patients with a poor outcome (25). However, this finding is contradictory to the earlier finding that seizure onset zone and interictal spike frequency measures may be useful in predicting the long-term seizure outcome on subdural electrocorticography (15). In addition, pathologic theta (76, 80-82) was suggested to be important in previous LFA studies (25, 33, 79). Therefore, previous LFA analyses in comparison HFAs (25) may be suboptimal or "underfitted" in identifying pathologic LFA activities related to seizure outcome especially in LFAs. Thus, we speculate that the clinical utility of LFAs need to be properly reinvestigated in comparison to HFAs. Extensive search of numerous thresholds using reinforcement machine learning from seizure outcome would be also effective in

improving currently suboptimal analysis in some studies especially in LFAs.

Cut-off frequency between HFAs and LFAs

In recent literature, the cut-off frequency between HFAs and LFAs was usually approximately 80 – 100 Hz (25, 33, 54). This was mainly because conventional electroencephalography usually investigated the band below 75 – 100 Hz. However, gamma below 100 Hz and RP above 100 Hz have similar inhibitory interneuronal mechanisms (22). We speculate that the band with equivocal relationship to seizure outcome may be identical to gamma-RP with the intermixed inhibitory interneuronal activities above 20 – 30 Hz in the macroelectrode ECoG (22, 60). Therefore, we suggest that the mechanism and seizure outcome oriented cut-off frequency between LFAs and HFAs may be identified from our study.

Main purpose of the study

The purpose of the present study is to elucidate characteristics of activities that are most significantly and reproducibly related to seizure outcome in both high and low-frequency ECoG. For this purpose, we combined several signal processing and machine learning methods and log-scale selection of frequency-bins (47, 61, 62, 83-87).

2 Methods

Subjects and epilepsy types

The present study was approved by the Institutional Review Board in Seoul National University Hospital (No. 1310-066-527). From October 2010 to February 2015, 39 patients (Table 1) with medically intractable NE underwent subdural electrode insertions for ECoG monitoring. Preoperative studies, the seizure outcomes, and resection percentage assessment methods were described in the previous studies (53, 76, 80). The seizure outcome groups were classified as seizure-free (International league against epilepsy (ILAE) classification I) or not-seizure-free groups (ILAE classification II – VI). The patients with neocortical temporal resections without

amygdalo-hippocampectomies were classified as NE and included in the present study. Callostomy patients without a volume resection were not included.

Electrocorticography analysis

The detection algorithm was shown in Fig 1. The analysis flow was shown in Fig 2. The electrocorticography (ECoG) sampling rate was 1,600 Hz. Custom MATLAB® (Mathworks™, Natick, MA, USA) programs were used in all analyses. We used in-memory computing in the custom MATLAB® program. The automatic detector used four kinds of thresholds (Fig 1) (53, 76, 80). We analyzed interictal periods containing interictal spikes or epileptiform rhythms individually selected by epileptologists, since interictal periods with epileptiform activities were suggested as important for both LFAs and HFAs (36, 88). Two interictal datasets of one minute each containing epileptiform activities during sleep without artifacts were selected for each patient. The first dataset, "training dataset", was used for the optimization of thresholds and the automatic detector training. The second dataset, "validation dataset", was used for retesting to evaluate the performance of the detector and remove overoptimized results (89).

Analysis in multiple frequency-bins, the spectral factor analysis

We divided the band from 0.9 to 600 Hz into 37 frequency-bins. We analyzed each frequency-bin separately to identify the bands that were significantly related to the seizure outcome. This analysis is similar to the spectral factor analysis described in literature (90). A single scale wavelet transform was used for each frequency-bin. Log-linear power scales increased by multiplying by a factor of 1.2 were used considering the log-linear frequency characteristics of neural oscillations (47). Logarithms were applied for the visualization of the time–frequency maps (44, 91).

The wavecluster detection method

The wavecluster method described in our previous study was used to detect ECoG activities (53). The wavecluster is a cluster in the wavelet transformed domain (85). First, ECoG activities

were clustered using complex Morlet wavelets with long temporal support during the wavelet transform (bandwidth parameter = 18, wavelet center frequency = 1). We used a narrow frequency support complex Morlet wavelet to improve the frequency resolution, and this issue is discussed in the Supplemental material 1. Second, continuous ECoG activities over the minimum amplitude threshold and below the maximum amplitude threshold were clustered and detected. We initially introduced the maximum amplitude threshold to remove the high-amplitude artifacts. Third, detected ECoG activities with a duration below the threshold were discarded. Fourth, the number of detected activities within the unit of time was counted, and the channels containing the number of activities exceeding the threshold were considered as having significant detections. Examples of these thresholds optimized using the genetic algorithm are shown in Table 2 and Fig 3. Examples of detections were shown in Figs. 4, 5 and 6.

Genetic algorithmic optimization for reinforcement learning from seizure outcome

The automatic detector thresholds were optimized using the genetic algorithm, since this method is theoretically more efficient than the Monte-Carlo method (92). Using the genetic algorithm, the optimization starts from a population of randomly generated threshold combinations. The performance of the detector using these thresholds is evaluated by the fitness function in each generation. The threshold combinations with better detector performance are selected stochastically in each generation. The thresholds are iteratively modified to find out the best threshold combinations (92).

The Matlab® function 'ga' was used. The genetic algorithmic optimization was used to minimize the fitness function as follows:

$$U_{SF} = R_{SF} - \frac{N_{SF}(N_{SF}+1)}{2}.$$

N_{SF} is the number of patients with detected pathological activities in the seizure-free group. R_{SF} is the rank sum of the resection percentages of detected pathological activities in the seizure-free group. This fitness function, U_{SF} is identical to the one-tailed U of the Mann-Whitney U test for

seizure-free group. Thus, we only consider the condition that $R_{SF} < R_{NSF,}$ the rank sum of the resection percentages of detected pathologic activities in the not-seizure-free group.

Thus, the optimization was done to achieve a statistically significant increase in the resection percentage of activities detected in seizure-free group compared to not-seizure-free patients. The reason for this was that our purpose was to establish detection thresholds that can significantly and accurately differentiate between the seizure outcome groups. The population size of each generation was 100, which was the number of threshold sets tested in each generation. The optimization was halted when there was no further decrement of the fitness function value during 10 generations. We tested 70,000 threshold combinations and found 6,000 optimized automatic detectors that can significantly differentiate among the seizure outcome groups ($p < 0.05$) in the training dataset. An example of optimized thresholds were shown in Fig. 3.

Prevention of overoptimization and validation

Because the detector was heavily optimized, overfitting or false positives after optimization should be an issue of concern. Thus, we used a simple detector (76, 80) with only four thresholds to reduce the model complexity and minimize the risk of overfitting (93). Therefore, the final risk of overoptimization was low in the present study.

Validation in a different patient groups

In addition, we also checked a test-retest reliability in the validation dataset (94) to rule out overoptimized results (93). To test reproducibility of our optimization results in a different patient group, we divided the total 39 patients into two groups. The detection thresholds were optimized to select pathologic activities which are related with better seizure outcome in the training dataset with 20 patients. We retested the mean values of detection thresholds in a completely different validation group with 19 patients. To compensate low number of patients, the augmented dataset with four samples per a patient was used. Half of the dataset was randomly selected for retests in various combinations of datasets to remove bias caused by

single fixed dataset.

Statistical estimation of the validation results

Using binomial distribution and potential false positive rate, 0.05 in the validation, we can calculate the probability according to the obtained number of significant results. We tested 30 kinds of optimized threshold combinations. The probability that there would be four significant results (blue horizontal line, Fig. 7) among 30 tests is 0.045. Thus, frequency-bin with more than six significant results (red horizontal line, Fig. 7) can be considered to be validated with significance. The probability that there would be six significant results among 30 tests is 0.047. Thus, frequency-bins with more than six results with tendency can be considered reproducible.

The resection percentage difference (Dif-R) between seizure outcome groups

The resection ratio was defined as the ratio between the number of channels in which seizure outcome-related pathological activities were detected and, among these, the number of channels that were inside the resected area (25, 95). A recent meta-analysis compared the resection ratios between seizure-free and not-seizure-free groups as a measure of the effect-size (95). The resection percentage was defined as the resection ratio × 100. We calculated the differences (Dif-R) in resection percentages among the seizure outcome groups for detected pathological activities (95). Dif-Rs are shown in selected frequency-bins (Figs. 8, 9 and 10). We only showed the examples from a few frequency-bins with abundant automatic detector optimization results that significantly differentiated among the seizure outcome groups in both the training and the validation dataset.

3 Results

Patient characteristics, follow-up and outcome

Patients' information is shown in Table 1. There were 39 NE patients with 23 male and 16 female patients. The mean age was 28.2 ± 6.8 years (12 – 55 years). There were 23 male and 16 female patients. The mean follow-up duration was 21 ± 11 months (13 to 44 months). Sixteen out of the 39 patients were seizure-free (41 %). The mean number of electrocorticographic channels per patient was 56 ± 21 (12 to 92 channels). The total number of channels was 2,190.

Detection examples in spectrograms and waveforms

Automatic detection examples were shown in Figs 4, 5 and 6.

Validation reproducibility in a different patient group

Validation results in a different patient group with original trained thresholds was shown in Fig 11. Delta in 2.0 – 2.3 Hz were reproducible. LFAs between 4.9 – 43 Hz including theta, alpha, beta and low-gamma were reproducible significantly. Low reproducibility in 52 Hz is an expected result from power line artifacts. Reproducibility of high-gamma in 62, 75, 108 and 322 Hz was significant. In LFAs, the resection of detected activities were positively related with better seizure outcome as intended (Fig. 7). However, high-gamma activities are paradoxically negatively related with seizure outcome (Fig. 7). LFAs had higher reproducibility and effect-sizes than HFAs.

Effect-size measured in resection percentage differences (Dif-R) among the seizure outcome groups in the validation dataset from different patients

Dif-R in the different 19 patient group was shown in Fig. 8 according to frequency-bins. Resection of detected activities are positively related to seizure outcome in LFAs and HFAs greater than 155 Hz. However, high-gamma and ripple band had negative Dif-Rs.

4 Discussion

Resection percentage differences (Dif-R) of HFAs and LFAs

Dif-Rs especially in LFAs in the validation dataset in the present study are comparable to Dif-Rs in HFAs in the training dataset without validation reported in the literature, 17 to 27 % (95). We first showed that data-mining based on the outcome of seizures can be comparable to up-to-date analysis performances even in the validation dataset from different patient group. This means that further applications of such a system may be useful in the future. Retesting the system using a different dataset shows that this method is also valid in a different condition (93).

Proper optimizations for LFAs and HFAs and clinical applications

Many studies exploring the HFAs have suggested that HFAs are more closely related to the areas of the seizure onset or the seizure outcomes than the LFAs that were represented as interictal spikes in most studies (25, 96). However, this result is different from a previous study where significant information relevant to the seizure outcome was provided by interictal LFAs (15). Thus, the studies exploring HFAs probably used suboptimal analysis methods for the analysis of LFAs (93). In contrast, we optimized the detectors using genetic algorithms, and applied identical methods for both HFAs and LFAs. Thus, we could compare HFAs and LFAs in relation to the seizure outcome under identical conditions. The results in the present study showed that LFAs can be related to the seizure outcome. Thus, we suggest that LFAs, the long-standing gold standard for epilepsy surgery (23), should be always considered in combination with HFAs. However, HFAs may be an important new biomarker considering high effect-sizes as suggested in most HFA studies as well as by our current data (25, 33, 45, 79).

Consistency of our results with previous studies and further applications

In previous studies, pathological theta activities (80-82), high-gamma (53), and fast ripple bands (25, 46, 76, 79) were significantly related to the seizure outcome. Using the present automatic

detector optimization method for wideband with little human supervision in this single data-mining study, we could evaluate the seizure outcome-related pathological activities in multiple bands suggested by various studies. These findings suggest the validity of the analysis, a wideband applicability, and powerful automation capability of the seizure outcome-based reinforcement learning methodology used in the present study. In addition, the found thresholds are very similar to a previously suggested threshold between pathologic and physiologic HFAs (52). The distinction between pathologic and physiologic HFAs is an important issue in the HFA analysis (97) and seizure outcome based analysis may help resolving this question. Pathologic and physiologic HFAs will be related with seizure outcome completely differently when resected.

Pathologic interictal theta activities

Theta activities were most significantly and reproducibly related to seizure outcome in this study. Theta outside the seizure onset zone supports the concept of widespread potential epileptogenic networks in the not-seizure-free groups, for example, *de novo* epileptogenesis, temporal lobe epilepsy and widespread networks (98-100). In this concept, the resection of zones currently generating the seizure is not sufficient for obtaining complete seizure freedom and additional resection or disconnection of zones with epileptiform activities and later epileptogenic potentials would improve long-term seizure outcome (98).

Reproducibility and effect-sizes in a different patient group

High-gamma activities are paradoxically negatively related with seizure outcome (Fig. 8) suggesting inhibitory or physiologic mechanisms. This is an unexpected and paradoxical result because the dectector was initially trained to detect pathologic activities which are positively related with seizure outcome. This finding suggests that the pathologic high-gamma and ripple and physiologic ones are very similar in amplitudes and numbers. Thus, detectors optimized to select pathologic high-gamma and ripples cannot rule out physiologic high-gamma and ripples which are very similar.

LFAs had higher reproducibility and effect-sizes than HFAs and potentially more useful clinically when neocortical ECoG is used. Dif-Rs in the retests in different interictal segments from the same patient groups were higher than literature which were evaluated only in the training dataset. Validation in a different patient group is more strict validation condition. Dif-Rs were similar to literature only analyzing in the training dataset without validation. This finding shows that our method is at least similar or superior in performances measured in Dif-R in comparison to previous methods.

Methodological comparisons between manual annotation based learning and automated, supervised seizure outcome-based reinforcement learning

Recently, great improvements of computer vision and deep learning were partially achieved by abandoning hand-crafted feature-based method and adopting fully automated learning based on the "ground truth", final classification results (101). Manual annotation results by experts in ECoG are similar to handcrafted features in computer vision in that these features are manually selected (66, 67). However, these annotations and handcrafted features represent only surrogate markers and the final outcome or the final classification result. Hence, the "ground truth" for machine learning should be adequately selected as the final outcome rather than manually selected surrogate markers. We stopped using manual annotations and only focused on final outcome of the seizures to train the automatic detector. By this method, with little human intervention, we could surpass the results of previous analyses (Figs. 7, 8 and 9). In this method, the characteristics of pathological activities are not designated by human experts. Instead, they are established by the machine learning.

Limitations of the methodology and further improvements

The detection method in the present study is simple, and all channels and frequency-bins are

analyzed separately. Combining multi-channel and cross-frequency information by spectro-spatio-temporal analysis (66, 102) and algorithms comprising recent developments of deep learning and network analysis (67, 70) may further improve the detector performance. However, these procedures would imply a greater number of optimization variables and higher risks of overoptimization that should be controlled adequately (93). Thus, as more complex algorithms would require more data for training and controlling overoptimizations, the data collected on 39 patients, the largest group analyzed according to the literature, may still not be sufficient. In addition, this is a macroelectrode based study. The results from microelectrode recordings may be different from different spatial summations of HFAs in macroelectrodes which may lower sampling effectiveness (40).

Further study plan to detect physiologic gamma-ripple activities

Most previous studies focused on finding pathologic HFAs including gamma-ripples (RP) s for better seizure outcome (36, 45, 73, 103). However, gamma-RP are mainly physiologic activities (104). Theoretically, if physiologic/inhibitory gamma-RPs signifying inhibitory restraints or "ictal penumbra" are preferentially detected by optimization, negative relationship between resection extents and seizure outcome might be found theoretically (58, 105). We firstly suggest that this theoretical negative relationship can be potentially identified from seizure outcome data by the data-mining. In this study, we investigate group only positively correlated between resection percentages and seizure outcome. If we investigate the groups negatively correlated between resection percentages and seizure outcome, it is theoretically possible to find inhibitory/physiologic activities.

However, the separation between pathologic and physiologic/inhibitory activities are a difficult task with generally low reproducibility and only partially achieved in this study. Our detector is relatively simple and further improvements of detectors are probably possible using cross-frequency coupling (36, 103). Our study firstly showed that it may be possible to avoid

inhibitory areas using inhibitory/physiologic HFAs may be possible in surgical planning (58, 105). However, this finding may also accrue to overoptimization and the underlying mechanism was speculated from clinical information (89). Therefore, further studies are warranted.

5 Conclusion

We suggest that an automatic analysis algorithm for ECoG can be effectively trained from epilepsy surgery outcome. By this method, a simple detector could outperform all manual or automatic analysis results in previous literature (95) in Dif-R. Thus, we suggest that the gold standard of pathologic HFA and LFA detections should not be the manual classification by experts, a surrogate marker but the association with postoperative seizure outcome, the final purpose of the ECoG analysis in the epilepsy surgery planning.

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국문 초록

데이터 마이닝에 기반한 신피질 뇌전증에서 예후와 관련된 두개강 내 뇌파 발작 간기 활동의 선택

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의학과 중개의학 과정

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배경 및 목적: 기존의 두개강내 뇌파상의 병적 활동의 자동화된 탐지 기법은 전문가의 판독에 의한 결과를 기준으로 시행되어 왔음. 그러나 본 논문에서는 뇌절제 수술 뇌전증 환자 수술 예후에 대한 강화 학습을 통해 자동화된 탐지 알고리즘을 향상시킴. 이 방법을 사용하여 뇌전증 환자에서의 발작간기 뇌파에서 저주파 및 고주파 활동을 분석함.

방법: 39 명의 난치성 신피질 뇌전증 환자와 26 명의 측두엽 뇌전증 환자에서 두개강 내 뇌파를 분석함. 병적 파형을 포함한 발작 간기 뇌파를 2개의 다른 구간에서 나누어서 수집함. 주파수 칸은 0.9 – 600 Hz 사이에서 37개로 분할하여 따로 분석됨. 자동 탐지 알고리즘은 단순하게 탐지할 뇌파 활동의 세기 범위와 길이, 개수에 등 4 가지 최적화가 필요한 변수만을 사용함. 따라서 과적합 (overfitting or overoptimization)의 가능성이 낮은 알고리즘이 사용되었음.

첫 번째 구간의 데이터에서는 자동 탐지 알고리즘을 수술 후 발작이 없는 환자군과 발작이 있는 환자 군 간에 탐지된 뇌파 활동의 절제 정도의 순위를 기준으로 가장 잘 분류하도록 최적화 됨. 두 번째 서로 다른 환자군에서 온 검증 데이터에서는 최적화된 탐지 알고리즘이 다시 평가되었음. 다른 환자군에서 분석

시의 재현성은 이산분포에서 기대되는 유의한 결과의 갯수를 통해서 계산함. 두 개의 데이터 군 간에 재현성이 있는 탐지 알고리즘으로 검증 데이터를 분석하였을 때의 수술 후 예후에 따른 환자 군 사이의 탐지된 뇌파 활동 부위의 절제 백분율의 차이 (Dif-R)이 파악됨. 그리고 전혀 다른 환자군에서의 재현성을 평가하기 위해 20 명의 환자군에서 최적화를 하고 다른 19 명의 환자에서 검증을 하는 분석을 하였음.
결과: 신피질 뇌전증 환자 중 16 명 (41 %) 은 수술 후 발작이 없었음. 신피질 뇌전증 환자의 수술 후 경과 관찰 기간은 21 ± 11 개월 (13 – 44 개월) 이었음. 최적화 이후 다른 19 명의 환자에서 재검증한 결과는 2.0 – 2.3 Hz의 델타 대역이 수술 후 예후와의 관련성에 있어서 재현성을 보였음. 세타, 알파, 베타, 낮은 주파수의 감마파를 포함하는 저주파 대역 4.9 – 43 Hz 도 유의한 재현성을 보였으며 높은 주파수의 감마, 62 와 75 Hz 및 고주파, 108 Hz 및 322 Hz 대역도 수술 후 예후와 유의한 연관성을 다른 검증 환자군에서 보임. 다른 환자군에서의 Dif-R은 10 – 20 % 가량이었음. 저주파 대역에서는 예상하였던 대로 탐지된 뇌파 활동의 절제 정도가 클 수록 예후가 더 좋은 상관 관계를 보임. 그러나 높은 주파수의 감마 대역은 이와 반대의 상관 관계를 보임.
결론: 수술 후 예후에 대한 뇌파 분석 기계 학습 알고리즘의 강화학습을 통해서 저주파 및 고주파 대역에서의 Dif-R (32 - 57 %) 을 기존의 고주파 대역에 대한 수동 및 자동 분석 방법 (17 - 27 %)을 넘어서는 수준으로 혹은 다른 환자군에서는 문헌과 유사한 수준으로 향상시킬 수 있었음. 따라서 본 연구에서는 기존의 해결이 어려운 문제인 뇌전증 수술 이후의 예후 향상을 위해서 본 알고리즘이 사용될 수 있다고 제안함.

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주요어 : 데이터탐색; 고주파활동; 수술 후 발작조절 예후; 저주파활동; 최적화; 효과크기

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Table 1 Clinical data of neocortical epilepsy patients including lateral temporal lobe epilepsy

Patient number	Age	Gender	MRI	Resection	Pathology[b]	Seizure outcome[a]
1	31	F	No lesion	L T	FCD Ib	1
2	27	M	No lesion	R F P	None	4
3	22	F	No lesion	L F P	None	1
4	25	F	Insula T2HSI	R T	Pilocytic astrocytoma, FCD I	3
5	23	M	No lesion	L P	None	4
6	30	M	No lesion	L F	FCD IA	4
7	34	M	No lesion	L P	None	4
8	30	M	No lesion, previous tissue defect	R P	FCD IIId	3
9	36	F	No lesion	R P	FCD Ia	3
10	36	M	Subependymal nodule	R P	FCD IIb	2
11	40	M	No lesion	R F	FCD I	1
12	18	M	Arachnoid cyst, left middle fossa	L T	FCD Ib	4
13	28	F	No lesion	R F	FCD Ia	4
14	15	F	No lesion	L F	None	1
15	25	M	No lesion	Callosotomy + R F	FCD Ia	1
16	27	M	No lesion	L O	FCD Ia	1
17	30	M	R F and cerebellar CM	R T O	FCD IIId	3
18	25	M	No lesion	R P	FCD Ia	4
19	29	F	L P O CM	L T P	FCD Ib	3
20	37	M	L O CM	L O	FCD Ia	3
21	37	F	Cerebellar CM	R P	FCD Ic	3
22	23	M	Unrelated bilateral F CM	L P	FCD Ib	2
23	43	M	Calcified lesion	L T	FCD IIId, R/O cavernous malformation	1
24	27	F	No lesion	R T O	FCD Ia	4
25	39	M	No lesion	L T	FCD Ic	1
26	19	F	No lesion	L F	FCD IIa	1
27	19	M	No lesion	R F	FCD IIa	1
28	33	M	R/O L HS	R F	FCD IIb	1
29	27	F	No lesion	L F	FCD Ib	5
30	31	M	L P CM	L P	FCD Ia	1
31	31	M	L T T2HSI	L T	FCD IIb	1
32	25	F	L F CM	L F	FCD IIId	1
33	22	F	L F CM	L F	Arachnoid cyst	1
34	38	F	L F CM	L F	FCD IIId	1
35	16	F	No lesion	R O	FCD IIa	4
36	26	M	R P O cyst	R O	Ganglioglioma	2
37	23	M	L T CM and T2HSI	L T	FCD Ia	1
38	26	F	No lesion	L P	FCD Ia	5
39	25	M	No lesion	R O	FCD IIa	1

a = The classification of the seizure outcome by the International League Against Epilepsy was used; b = The three-tiered International League Against Epilepsy classification system of focal cortical dysplasia by Blumcke in 2011; CM = cerebromalacia; F = frontal; FCD = focal cortical dysplasia; HS = hippocampal sclerosis; T2HSIL = high signal intensity lesion in T2 weighted MRI; L = left; O = occipital; P = parietal; R = right; T = temporal

Table 2 Examples of detection thresholds among the selected frequency-bins

Frequency (Hz)	Amplitude thresholds[a]		Minimum duration threshold (ms)	Number threshold (/s)	Mean Dif-R% difference between seizure outcome groups	P-values between seizure outcome groups
	Low	High				
321	2.8	10.3	3	107	32	0.02
268	5.3	11.0	15	18	50	0.04
223†	4.3	8.4	1	220	53	0.01
223†	4.7	7.8	11	21	49	0.02
90	3.6	9.4	5	103	55	0.04
90‡	4.0	8.7	18	83	73	0.02
75	3.1	8.5	14	81	54	0.02
30	3.3	9.8	17	38	62	0.01
21†	2.1	8.3	85	47	34	0.03
21†	2.4	8.4	243	18	34	0.03
17	2.1	8.5	286	19	32	0.04
12	1.5	10.2	572	9	15	0.03
10	1.1	7.8	643	21	35	0.03
7	2.4	6.9	325	7	25	0.03
5.8	1.6	6.6	983	7	20	0.03
4.9	2.0	8.3	426	6	20	0.03
4.0†	1.6	5.4	652	9	29	0.01
4.0†‡	1.4	10.6	1956	8	81	0.048
2.3	1.4	8.2	283	5	19	0.04

*Seizure outcome groups were differentiated by these thresholds with $p < 0.05$ in both the training dataset and retests in the validation dataset. [a] Root mean square amplitude of all channels × high amplitude threshold > Amplitudes of the detected activities > Root mean square amplitude of all channels × low amplitude threshold; †Two kinds of optimizations were listed in a single frequency-bin to show certain variations in the detection thresholds, especially the reciprocal changes in duration and the number thresholds. ‡These are the examples of the maximum Dif-R detector thresholds in each frequency-bin. The maximum Dif-R detections are highly specific, and many patients are excluded from non-significant

detections due to high detection thresholds.

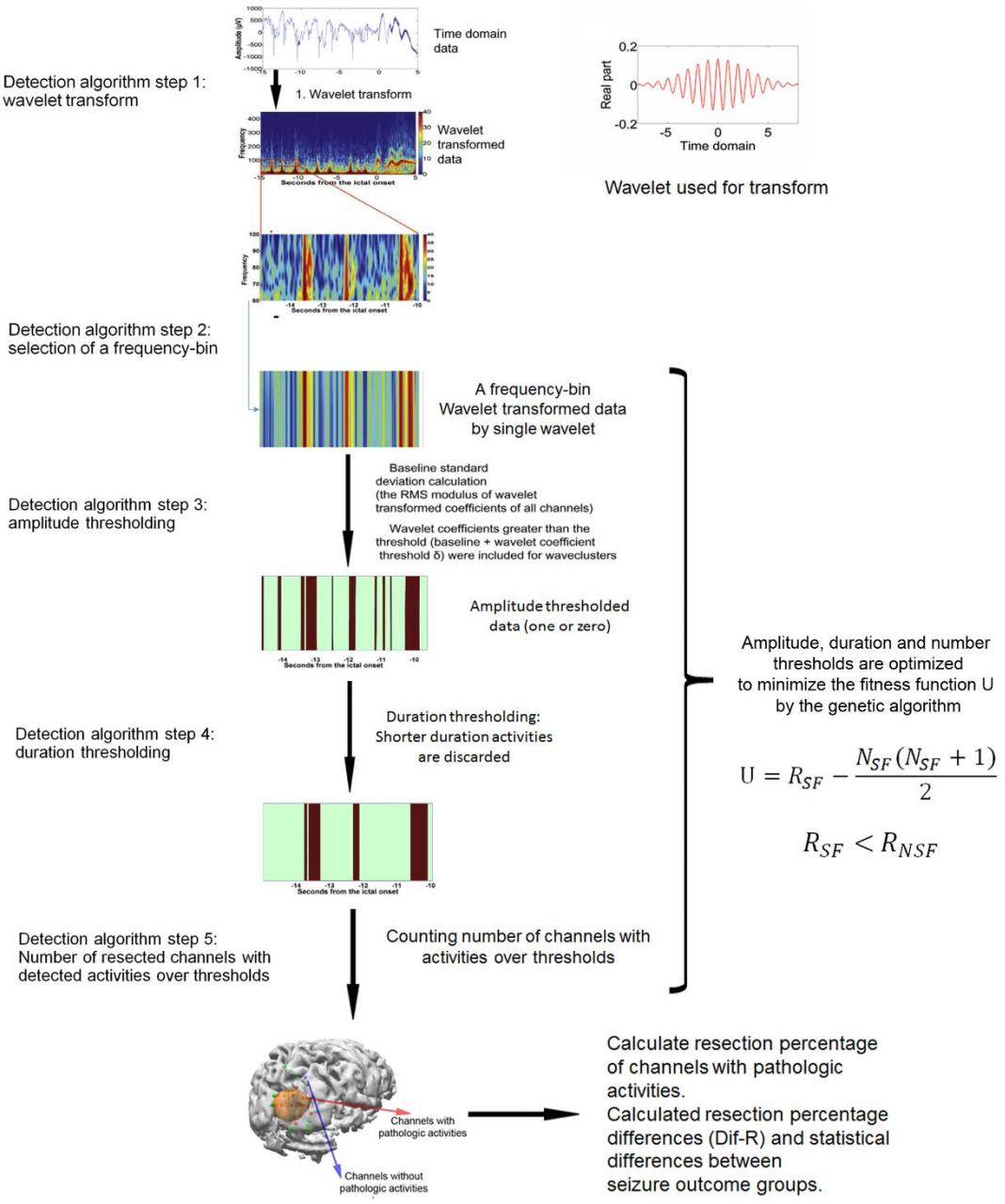

Figure 1 The automatic detection method and the calculation of Dif-R. Each frequency-bin is analyzed separately. Activities are detected using amplitude, duration and number thresholds. Thresholds are optimized using genetic algorithm to minimize U achieving highest statistical

differences of rank sum of resection percentages of detected activities between seizure outcome groups. N_{SF} is the number of patients with detected pathological activities in the seizure-free group. R_{SF} is the rank sum of the resection percentages of detected pathological activities in the seizure-free group. This fitness function, U_{SF} is identical to the one-tailed U of the Mann-Whitney U test for seizure-free group. Thus, we only consider the condition that $R_{SF} < R_{NSF,}$ the rank sum of the resection percentages of detected pathologic activities in the not-seizure-free group. After optimization, Dif-Rs were evaluated in the validation dataset. High Dif-R means the large resection extent difference of detected activities between seizure outcome groups.

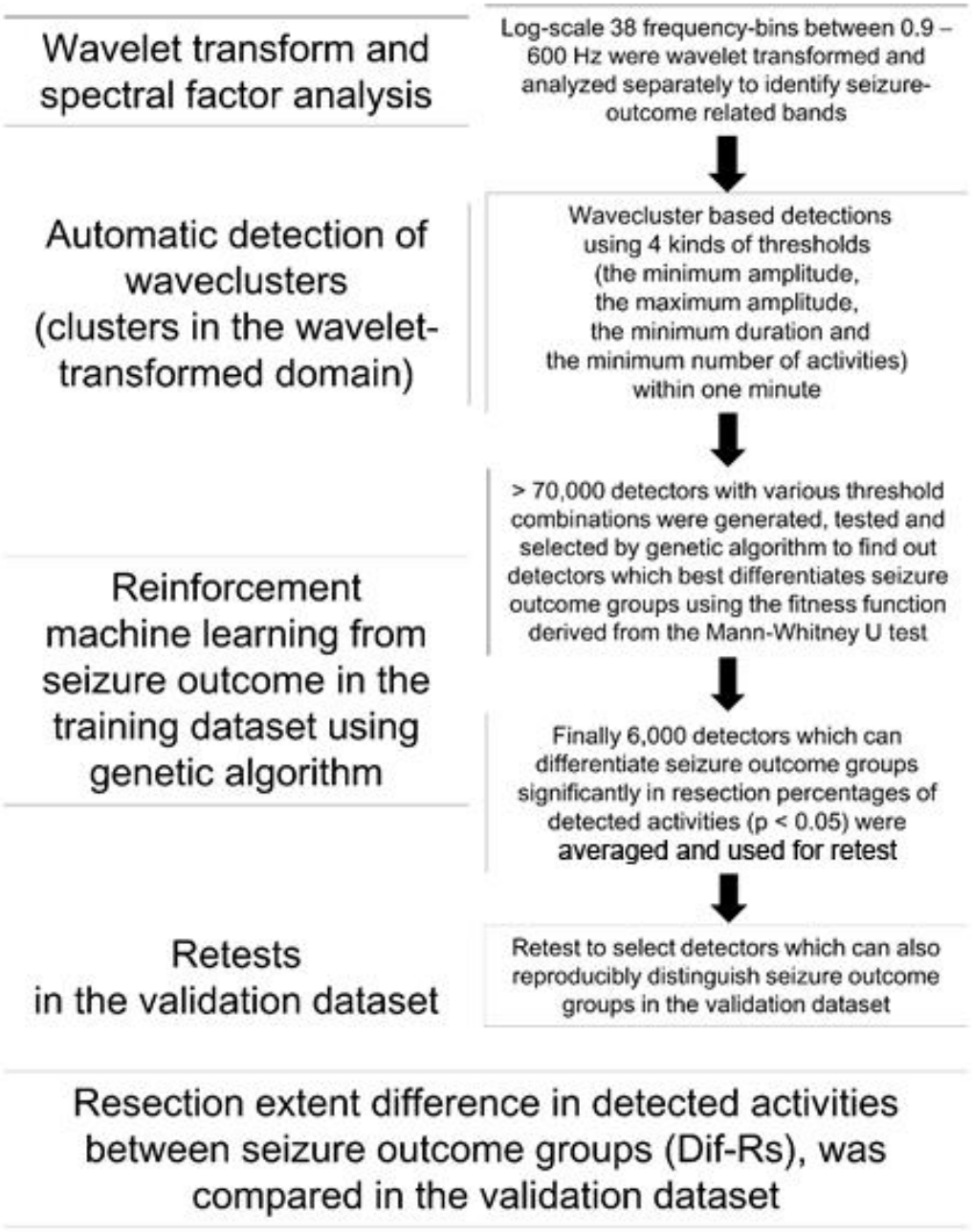

Figure 2 The analysis flow using the reinforcement machine learning based on the seizure outcome

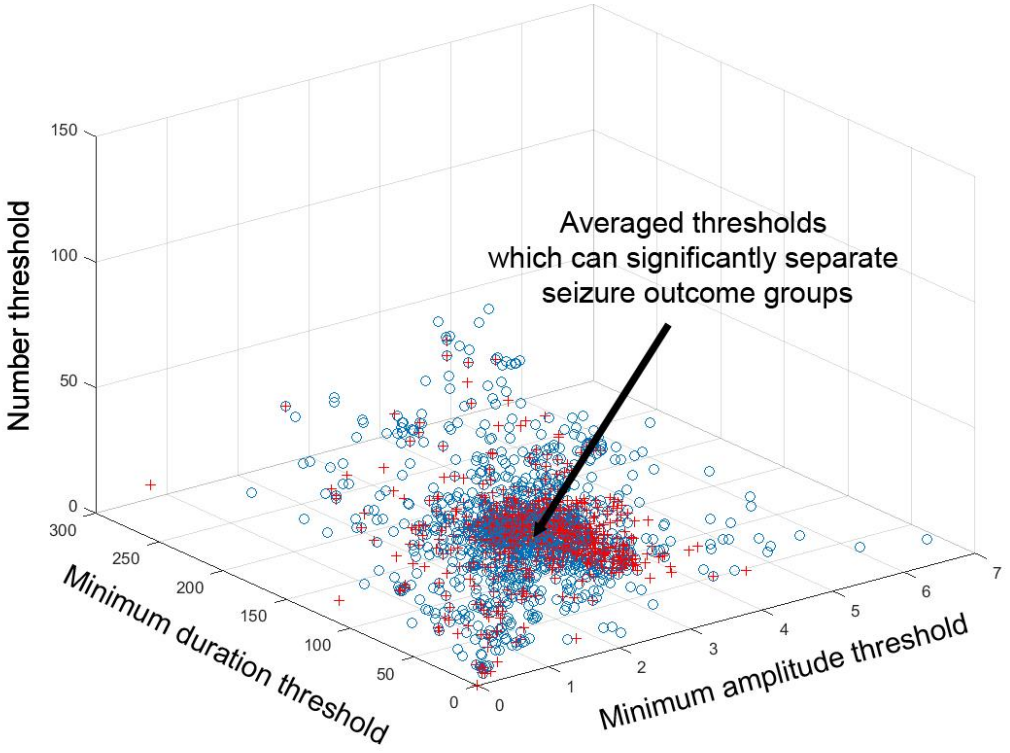

Figure 3 Detection thresholds tested during the genetic algorithmic optimization in 43 Hz frequency-bin. Red crosses are threshold combinations which could significantly distinguish seizure outcome groups based on resection percentages of detected activities ("significant thresholds", $p < 0.05$). Blue circles are threshold combinations which could not ($p > 0.05$). The cluster of significant threshold combinations was not multiple. Thus, we simply averaged all significant thresholds. We used the averaged threshold in a different validation patient group to check reproducibility.

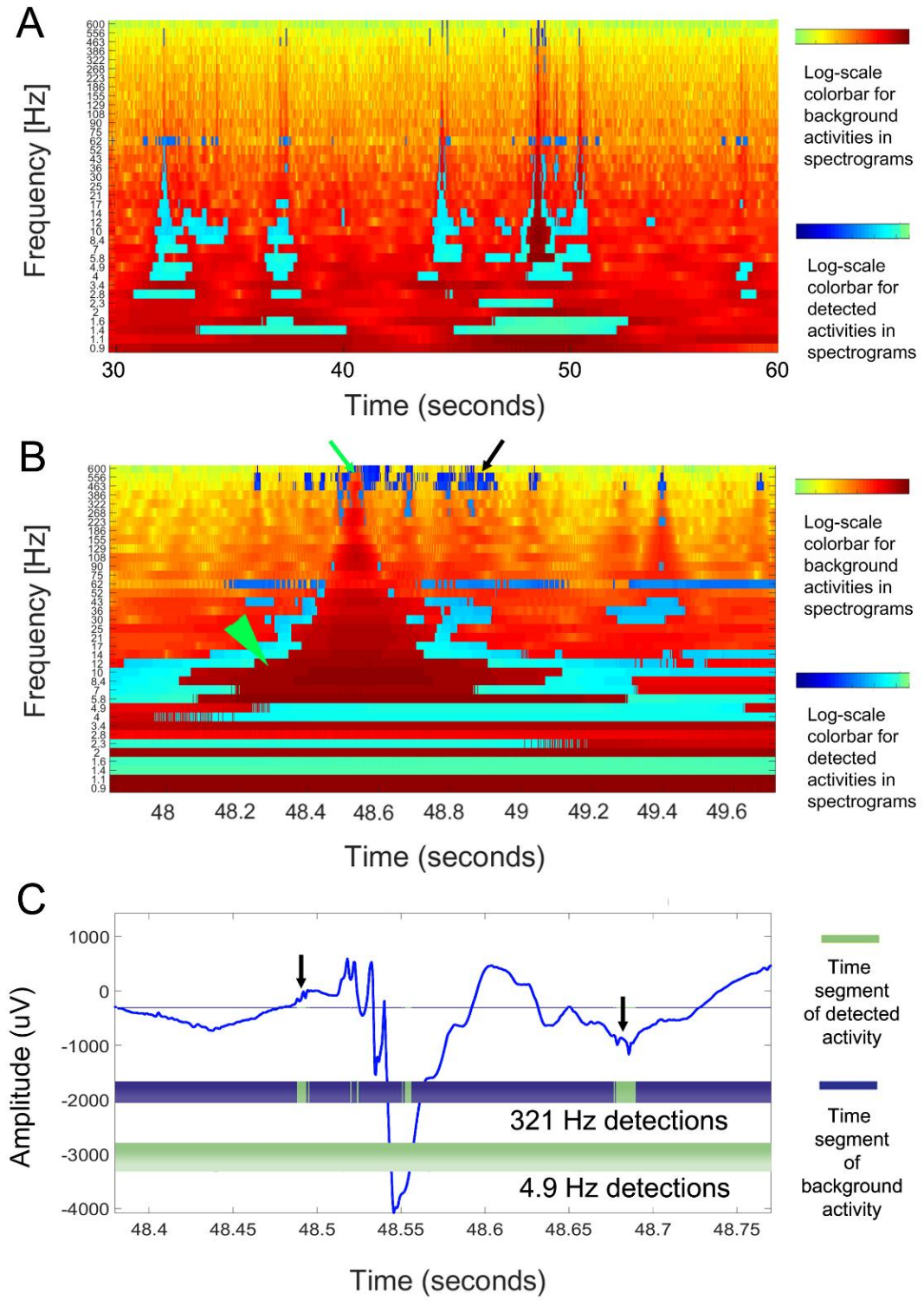

Figure. 4 (A) Detections in multiple frequency-bins in spectrograms in the interval between 30 – 60 seconds of the selected interictal segment. Data from the frontal channel in the patient 27 in

Table 1 is shown. Multiple broadband activities that can be visualized as spikes accompanying HFAs and LFAs are shown in Figure 4C. Detections in the 62 Hz are power-line artifacts. (B) A magnified spectrogram in 48 – 49.6 second interval offering a better identification of the details of HFA and LFA detections. Bandpass filtered broadband HFAs are excluded from the high amplitude thresholds (green arrow). Very-high amplitude LFAs are divided into two separate activities by high amplitude thresholds increasing the total number of detections (green arrowhead). The temporal patterns of HFA detections were different from those of LFAs (black arrow). This finding suggests that detected HFAs are not bandpass filtered artifacts of LFAs and distinct activities. (C) The waveform and detected activities in 4.9 and 321 Hz frequency bin. During 0.01 seconds, several oscillations in the unfiltered waveform can be identified suggesting the activity frequency of approximately 200 – 400 Hz (black arrows). These detections are not coincident with a high-amplitude spike suggesting that these are not bandpass filtered artifacts (Benar et al., 2010). The patient was seizure-free after the operation, and the pathology was focal cortical dysplasia type IIA.

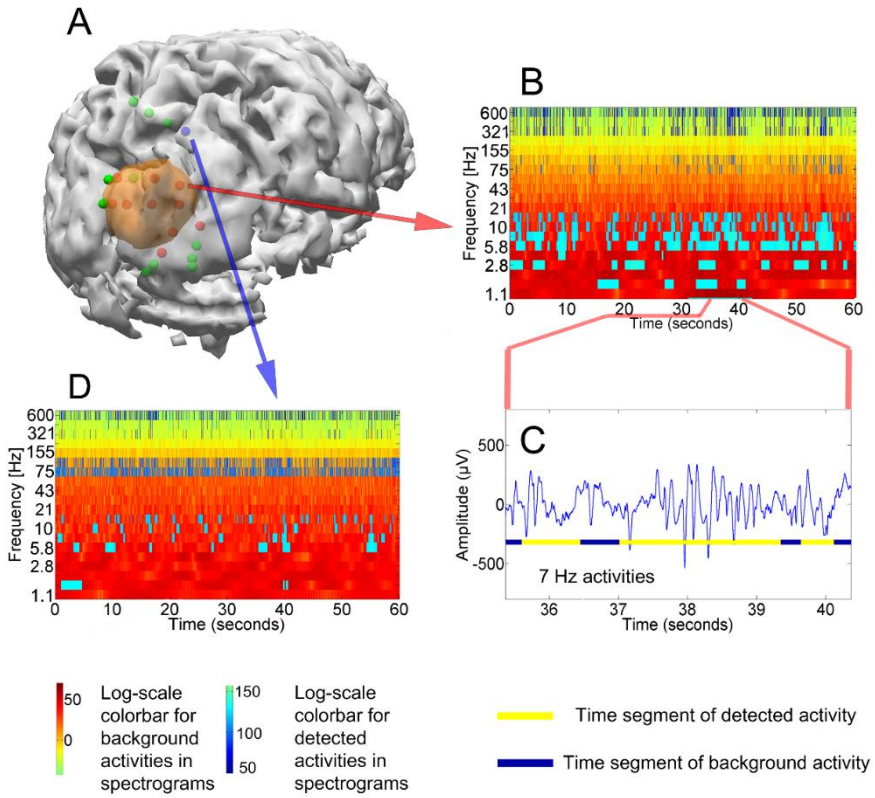

Figure 5 An example of surgical resection and the channels with pathological ECoG activities and seizure outcome. A seizure-free patient (the patient 39 in Table 1) is shown. (A) A three-dimensional fusion of 3 images including preoperative MRI, post-implantation CT for the electrodes, and post-resection MRI for the resection extent, was co-registered and visualized using Curry software (Compumedics® NeuroscanTM, Victoria, Australia). The orange shaded area indicates the resection volume. Small red spheres indicate the electrodes with pathological activities that were reproducibly related to a good seizure outcome when resected. Green spheres indicate the electrodes without a significant number of activities. Only ECoG electrodes implanted in the medial surface of parieto-occipital lobes are shown for clarity purposes. In this patient, pathological activities were mostly resected resulting into a seizure-free outcome. The pathology was focal cortical dysplasia type IIa. (B) Detection examples in a spectrogram within the resection volume. There were abundant pathological LFAs and HFAs in 321 Hz. (C) The magnified waveform and theta detections. (D) Detection examples in a spectrogram outside the resection volume (blue sphere and blue arrow). There were less detections of LFAs and HFAs.

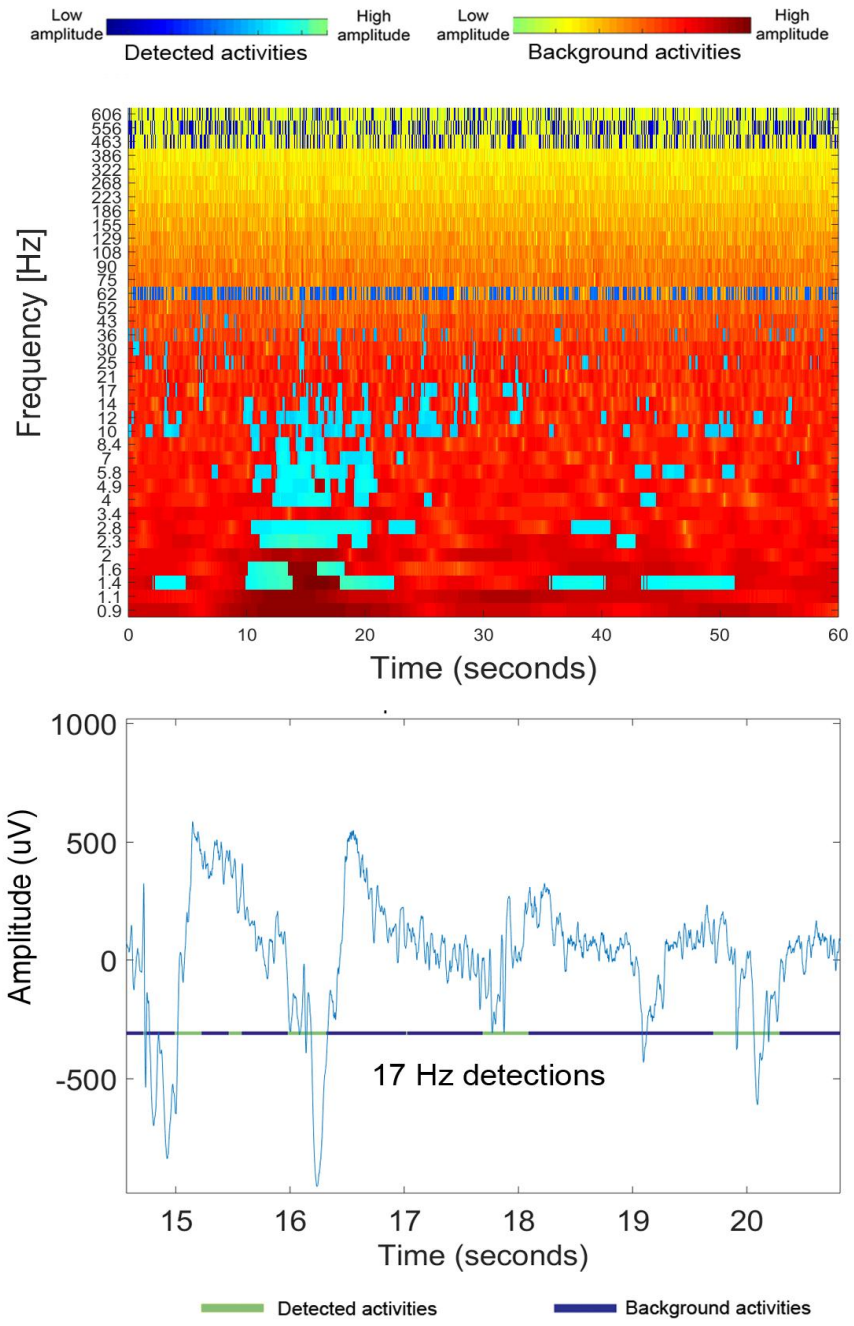

Figure 6 The upper figure: Detection examples in spectrograms of a left frontal lobe epilepsy patient. A left frontal channel was shown. The lower figure: 17 Hz detection examples in waveforms. the patient became seizure-free after left frontal resection.

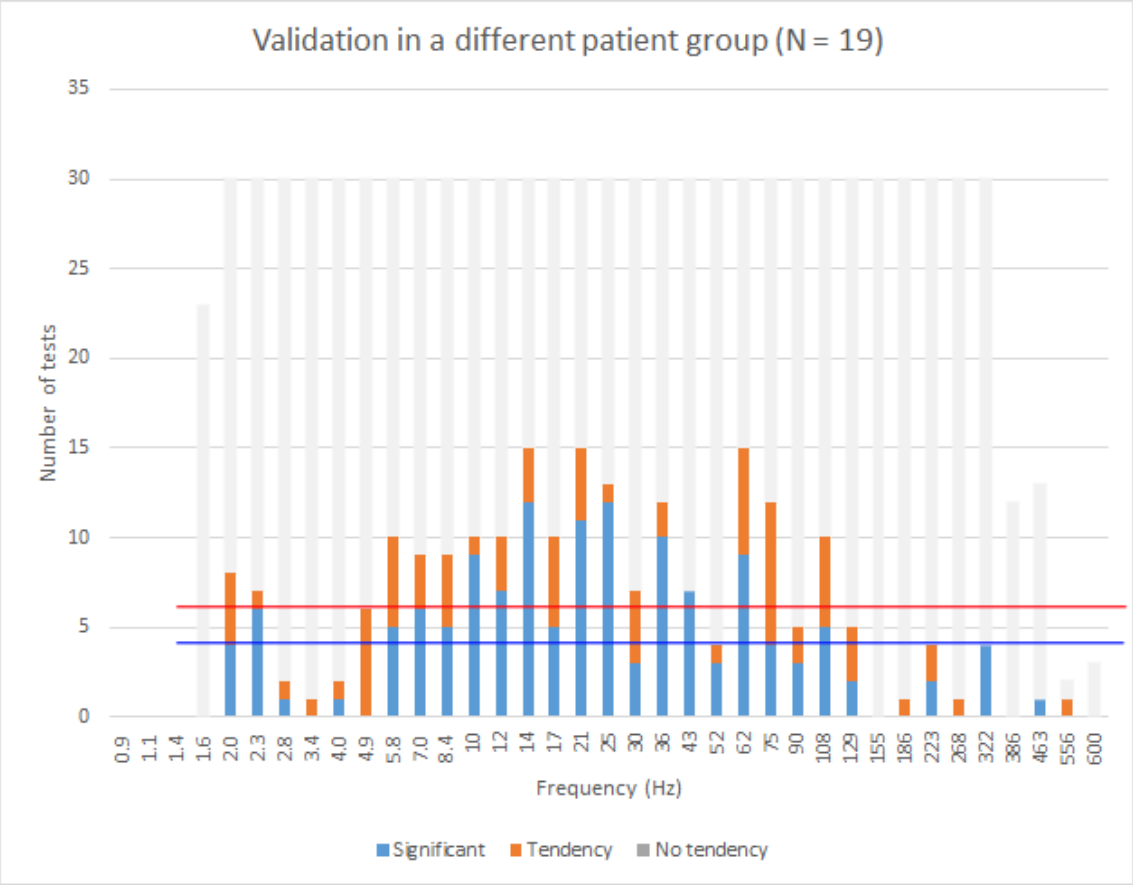

Figure 7 For each frequency-bin, 30 kinds of optimized automatic detectors which could separate seizure outcome groups in the training dataset was applied for the validation dataset with a different 19 patient group. Blue bars are significant results with $p < 0.05$ in the validation dataset. Orange bars are results with tendencies with $0.05 < p < 0.1$. Using the binomial distribution, the probability that there would be four significant results (blue horizontal line) among 30 tests is 0.045. Thus, frequency-bin with more than six significant results (red horizontal line) can be considered to be validated with significance. The probability that there would be six significant results among 30 tests is 0.047. Thus, frequency-bins with more than six results with tendency can be considered reproducible. Using this criterion, delta in 2.0 – 2.3 Hz were reproducible. LFAs between 4.9 – 43 Hz including theta, alpha, beta and low-gamma were most reproducible.. Reproducibility of high-gamma in 62, 75, 108 and 322 Hz seems to be present. However, high-gamma activities are paradoxically negatively related with seizure outcome (Fig. 8).

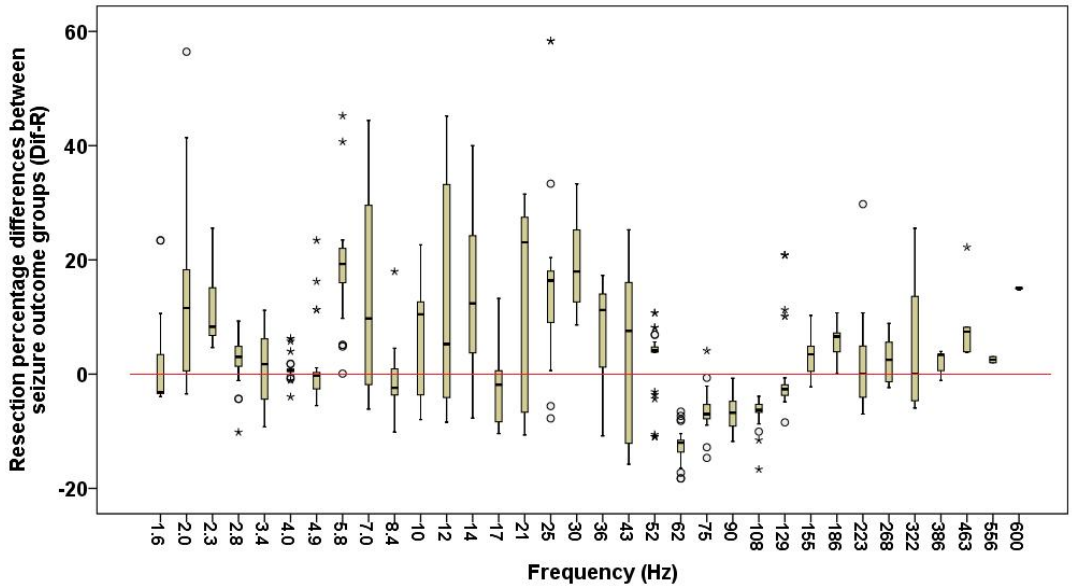

Figure 8 Resection percentage differences among the seizure outcome groups (Dif-Rs) in the different 19 patient group in all investigated frequency-bins. The detection thresholds that could significantly differentiate seizure outcome groups in the training dataset was applied for the validation dataset from a completely different patient group. Each boxplot is the summary of all detectors optimized in a frequency-bin. The upper and lower margins of the boxplots are the 25 % and 75 % quartiles. The whiskers are 1.5 times of the interquartile range. The circles are the outliers detected within 3 times of the interquartile range. The asterisks are the outliers detected beyond 3 times of the interquartile range. Resection of detected activities are positively related to seizure outcome in LFAs and HFAs greater than 155 Hz. However, high-gamma and ripple band had negative Dif-Rs suggesting inhibitory or physiologic mechanisms. Dif-Rs in the retests in different interictal segments from the same patient groups were higher than literature which were evaluated only in the training dataset. Validation in a different patient group is more strict validation condition. Dif-Rs were similar to literature only analyzing in the training dataset without validation. This finding shows that our method is at least similar or superior in performances measured in Dif-R in comparison to previous methods.