Automatic detection of intracranial High Frequency Oscillations by time-frequency analysis in epileptic patients

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SERGEY BURNOS

Master of Science in Financial Mathematics,
Halmstad University, Sweden
born on 28.01.1988
citizen of the Russian Federation

accepted on the recommendation of

Prof. Dr. R. H. R. Hahnloser
Prof. Dr. Martin Wolf
PD Dr. Johannes Sarnthein

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Abstract

For patients with therapy-refractory focal epilepsy, neurosurgical resection of the epileptogenic zone is a therapeutic option. In current practice, the location of the epileptogenic zone is identified by the seizure onset zone, defined by presurgical analysis of intracranial EEG.

Over the last years, high frequency oscillations (HFOs) have been proposed as a new biomarker for the epileptogenic zone. Since visual analysis is highly time-consuming for the expert reviewers, several automated algorithms for detection of HFOs in EEG signals have been proposed. The main focus of this thesis is on developing automated algorithms for detection of HFOs and their evaluation on clinical data.

The thesis begins with an introduction historical development and modern techniques for planning epilepsy surgery and what the HFO analysis can add to clinical diagnostics in order to improve the quality of life of epilepsy patients.

In Chapter 2, we proposed new automated detector that analyzes the instantaneous power spectrum of an individual HFO using the Stockwell Transform. The seizure onset zone - as defined in the presurgical workup - served as the gold standard. We showed that the detector is able to detect an HFO area that overlaps well with the SOZ.

In Chapter 3, we implemented automated algorithms for separation of HFOs from sharp epileptic spikes on simulated data. We proved the existence of two separate classes.

Chapter 4 covers further developments of the detector. It was also evaluated with respect to the surgical outcome on a set of patients different from the one it had been developed on. The detector was trained, validated and tested on a visually marked set of HFOs, and was compared to the existing detectors.

In Chapter 5, the automated HFO detector was evaluated with respect to the seizure outcome after the neurosurgical resection. We analyzed the HFO rates with respect to the sites of resection in order to evaluate the predictive value of the HFO detector.

The results of the research have direct impact on the treatment that is offered to epilepsy patients. While treatment is still based on established methods, a complementary biomarker like HFOs may aid in surgical decisions in ambiguous cases. The automated HFO detector described in this thesis has a potential to improve the post-surgical outcome of epilepsy patients.
Kurzfassung

Bei Patienten mit therapieresistenter fokaler Epilepsie ist eine neurochirurgische Resektion der epileptogenen Zone eine therapeutische Option. In der gegenwärtigen Praxis wird mithilfe einer präoperativen Analyse eines intrakraniellen EEGs die Anfallsursprungszone als epileptogene Zone identifiziert.

In den letzten Jahren wurden Hochfrequenz-Oszillationen (HFO) als neuer Biomarker für die epileptogene Zone vorgeschlagen. Da die visuelle Analyse für die Gutachter sehr aufwendig und zeitintensiv ist, wurden mehrere automatisierte Algorithmen zur Erkennung von HFO in EEG-Signalen diskutiert. Der Schwerpunkt dieser Arbeit liegt darin, automatisierte Algorithmen für die Erkennung von HFO zu entwickeln und klinische Daten auszuwerten.

Die Doktorarbeit beginnt mit einer Einführung in den geschichtlichen Hintergrund und in die modernen Techniken zur Planung der Epilepsiechirurgie und was die HFO-Analyse zur klinischen Diagnostik beitragen kann, um die Lebensqualität von Epilepsie-Patienten zu erhöhen.

Im Kapitel 2 haben wir einen neuen automatisierten Detektor eingeführt, der das instantane Leistungsspektrum einer einzelnen HFO mit der Stockwell-Transformation analysiert. Die Anfallsursprungszone - wie in der präoperativen Analyse definiert - diente als Goldstandard. Wir zeigten, dass der Detektor in der Lage ist, mittels HFO die Anfallsursprungszone zu erkennen.

Im Kapitel 3 haben wir die Algorithmen zur Trennung der HFO von scharfen epileptischen Spikes auf synthetische Daten angewendet. Wir konnten die Existenz von zwei getrennten Klassen bestätigen.

Das Kapitel 4 behandelt die Weiterentwicklung des Detektors und dessen Anwendung auf einen neuen Datensatz. Der Detektor wurde trainiert, validiert, mit einem visuell markierten Satz von HFO getestet und mit den bestehenden Detektoren verglichen.

Im Kapitel 5 wurde der HFO Detektor in Bezug auf die Anfallsfreiheit der Epilepsie-Patienten nach dem chirurgischen Eingriff evaluiert. Wir analysierten die HFO-Raten in Bezug auf den Resektionsbereich um den prädiktiven Wert des HFO-Detektors zu bestimmen.

Die Forschungsergebnisse haben einen direkten Einfluss auf die Behandlung, welche Epilepsie-Patienten angeboten wird. Während die Behandlung weiterhin auf etablierten Verfahren basiert, kann ein neuer Biomarker wie die HFO in Zweifelsfällen bei chirurgischen Entscheidungen als zusätzliche Informationsquelle dienen. Der automatisierte HFO-Detektor, der in dieser Arbeit vorgestellt wird, hat das Potential, das postoperative Outcome von Epilepsie-Patienten zu verbessern.
### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>EKG</td>
<td>Electrocardiography</td>
</tr>
<tr>
<td>EEG</td>
<td>Electroencephalography</td>
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<tr>
<td>EoI</td>
<td>Event of Interest</td>
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<tr>
<td>ETE</td>
<td>Extratemporal epilepsy</td>
</tr>
<tr>
<td>EZ</td>
<td>Epileptogenic zone</td>
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<tr>
<td>FCD</td>
<td>Focal cortical dysplasia</td>
</tr>
<tr>
<td>fMRI</td>
<td>Functional magnetic resonance imaging</td>
</tr>
<tr>
<td>FN</td>
<td>False negative</td>
</tr>
<tr>
<td>FP</td>
<td>False positive</td>
</tr>
<tr>
<td>FR</td>
<td>Fast ripple</td>
</tr>
<tr>
<td>FRandR</td>
<td>Fast ripple co-occurring together with ripple</td>
</tr>
<tr>
<td>HFO</td>
<td>High frequency oscillations</td>
</tr>
<tr>
<td>HS</td>
<td>Hippocampal sclerosis</td>
</tr>
<tr>
<td>iEEG</td>
<td>Intracranial EEG</td>
</tr>
<tr>
<td>ILAE</td>
<td>International league against epilepsy</td>
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<tr>
<td>LFO</td>
<td>Low-frequency oscillation</td>
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<tr>
<td>NPV</td>
<td>Negative predictive value</td>
</tr>
<tr>
<td>nRA</td>
<td>Not resected area</td>
</tr>
<tr>
<td>PPV</td>
<td>Positive predictive value</td>
</tr>
<tr>
<td>RA</td>
<td>Resected area</td>
</tr>
<tr>
<td>ROC</td>
<td>Receiver operating characteristic</td>
</tr>
<tr>
<td>sAHE</td>
<td>selective amygdala-hippocampectomy</td>
</tr>
<tr>
<td>SOZ</td>
<td>Seizure onset zone</td>
</tr>
<tr>
<td>TLE</td>
<td>Mesial temporal lobe epilepsy</td>
</tr>
<tr>
<td>TN</td>
<td>True negative</td>
</tr>
<tr>
<td>TP</td>
<td>True positive</td>
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Curriculum Vitae

1988
Born in Magadan, USSR

2005-2009
Bachelor’s program in Applied Mathematics and Computer Science
Volgograd State University, Russia

2009-2011
Master’s program in Financial Mathematics
Halmstad University, Sweden

From 2012
Ph.D. at Dept. of Information Technology and Electrical Engineering, ETH Zürich
International Ph.D. Program in Neuroscience, Neuroscience Center Zurich
Joint research between
1) Neurosurgery Department, University Hospital Zurich
2) Institute of Neuroinformatics, University of Zurich and ETH Zurich
3) Swiss Epilepsy Center, Zurich
Scientific contribution

Journal articles


* These authors contributed equally to the work.

Conferences and talks

1. The 3rd SFCNS Congress, 2016, Basel, poster, “Automated detection of high frequency oscillations predicts seizure freedom in individual patients”
2. The 12th symposium of the ZIHP, 2016, Zurich, poster, “Automated detection of high frequency oscillations predicts seizure freedom in individual patients”
3. The 15th Day of Clinical Research, 2016, Zurich, poster, “Relation of automatically detected HFOs with the SOZ and clinical outcome”
4. The 2nd International Workshop on HFOs, Freiburg, Germany, talk, “Relation of automatically detected HFOs with the SOZ and clinical outcome”
5. The 2nd International Workshop on HFOs, Freiburg, Germany, poster, “The morphology of high frequency oscillations does not improve delineating the epileptogenic zone”
6. The 31st IEC conference, 2015, Istanbul, Turkey, poster, “The morphology of high frequency oscillations does not improve delineating the epileptogenic zone”
7. INI lab meeting, 2015, Zurich, talk, “The morphology of high frequency oscillations does not improve delineating the epileptogenic zone”
8. INI lab meeting, 2014, Zurich, talk, “Classification of HFOs in stimulated data and patient EEG”
10. SSN conference, 2014, Zurich, talk, “Human intracranial High Frequency Oscillations (HFOs) detected by automatic time-frequency analysis”
12. INI lab meeting, 2014, Zurich, talk, “Human intracranial High Frequency Oscillations (HFOs) detected by automatic time-frequency analysis”
13. The 11th symposium of the ZIHP, 2013, Zurich, talk, “Markers of the epileptogenic zone: automatic detection of High Frequency Oscillations (HFOs) in the time-frequency domain”
14. ZNZ symposium, 2013, Zurich, poster, “Human intracranial High Frequency Oscillations (HFOs) detected by automatic time-frequency analysis”
15. INI lab meeting, 2013, Zurich, talk, “Detection of High Frequency Oscillations (HFOs) in intracranial recordings of epilepsy patients”

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4. The 3rd SFCNS Congress, the 2nd Poster Prize, Basel, 2016
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Chapter 1. Introduction

Epilepsy is the most frequent serious neurological disorder, affecting people of all ages (World Health Organization, 2005). Every tenth person in the world has at least one epileptic seizure in his lifetime, and a third of these develop epilepsy. At any moment, 1% of the total world’s population has active epilepsy. Despite a vast increase in the number of antiepileptic drugs made available over last years, at least 40% of patients with epilepsy fail to become seizure free with medical treatment (Lüders et al., 2006).

For these patients there is an option to surgically remove part of the brain, which is responsible for generating seizures. This area is called epileptogenic zone (EZ, Figure 1.1) and defined as the minimum amount of cortex that must be resected (inactivated or completely disconnected) to produce seizure freedom (Lüders et al., 2006).

Epilepsy surgery aims at the removal of epileptic brain tissue to achieve seizure freedom. Currently, large epilepsy centers report average seizure free rates of 60-90% (Wiebe et al., 2001; Engel et al., 2003). Therefore, considering the severity of the epilepsy in the population operated on, the methods for identification of the EZ should be improved in order to consider epilepsy surgery as a very successful therapy.

1.1 Historical development of epilepsy surgery

Sir Victor Horsley, a British neurosurgeon, was first who performed epilepsy surgery and, in 1886, published the reports on successful resections of cortical tissue, which resulted in a significant reduction of epileptic seizures in three patients (Horsley, 1886). In 1929, H. Berger (Berger, 1929) published the first study on electroencephalography (EEG) recordings in humans from outside the skull. Few years later in 1934 O. Förster (Förster and Altenburger, 1934) reported the first intracranial EEG (iEEG), which was recorded directly from the exposed surface of the human brain.

Nevertheless, until 1950s the boundaries of the EZ were defined exclusively by the extent of the macroscopical cortical lesions.

In the early 1950s, Bailey and Gibbs (Bailey and Gibbs, 1951) and Penfield and Jasper (Penfield and Jasper, 1954) additionally used complementary scalp and intracranial EEG, recorded between seizures (interictal), to estimate the limits of the EZ.

For the next 20 years these tools played the essential role to define the EZ, even though researches realized the limitations and lack of precision of the interictal epileptiform activity as a marker of the EZ (Lüders et al., 2006).

A novel discovery was the introduction of the stereo-EEG by Jean Talairach and Jean Bancaud that reformed the concept of the EZ (Talairach and Bancaud, 1973). Talaraich and Bancaud recorded electrical activity of the suspicious brain areas during epileptic seizures
Therefore, they assumed that this methodology is ideal to define the EZ with extreme precision.

### 1.2 Modern techniques for planning epilepsy surgery

The objective of epilepsy surgery is the complete resection or complete disconnection of the epileptogenic zone. This aim needs to be achieved with preservation of the “eloquent” cortex – specific brain areas that directly controls function, thus damage to these areas generally produces neurological deficits.

Modern epileptologists use a variety of diagnostic tools, such as analysis of seizure semiology, EEG recordings (scalp and intracranial), functional testing and neuroimaging techniques to precisely define the location of the EZ. These diagnostic methods define different cortical zones (area of interictal epileptic spikes, seizure onset zone (SOZ) and the epileptogenic lesion), each of which is a more or less precise marker of the location and extend of the EZ (Figure 1.1). The ability to define the EZ precisely is essentially a function of the sensitivities and specificities of the diagnostic methods (Rosenow and Lüders, 2001).

![Figure 1.1 Adaptation of the presurgical model of Rosenow and Lüders and of Jacobs et al. (Rosenow and Lüders, 2001; Jacobs et al., 2012). Studies about the correlation between HFO removal and post-surgical seizure outcome shows that HFOs may be able to measure the epileptogenic zone (red).](image)

Interictal epileptic spikes occur in the epileptic brain and can be useful for diagnostics. However, neurosurgeons cannot fully rely on them, as these spikes can be recorded in the EEG of a small percentage of healthy volunteers and relatively larger percentage of patients without a history of seizures (So, 2010).

Epileptic seizures themselves are a specific biomarker of epileptogenicity, although due to their unpredictable nature and irregular occurrence, ictal EEG recordings are not ideal in terms of time, cost and clinical risk for presurgical evaluation. Nowadays, iEEG recorded during ictal periods is routinely used to define the seizure onset zone (SOZ), which is the current gold standard for localization of the EZ. The SOZ is the area of the brain from which epilepsy seizures are actually generated, as opposed to the EZ, which is the area of the brain that is indispensable for the generation of epileptic seizures. However, removal of the SOZ and areas of interictal spiking does not always lead to a reduction of seizures after surgery. This is probably caused by a sub-optimal detection of the epileptogenic tissue, and sensitive biomarkers for the detection of epileptogenic tissue are therefore much needed (Jacobs et al., 2012; Zijlmans et al., 2012b).
1.3 High frequency oscillations as biomarkers of the epileptogenic zone

First recordings of spontaneous high frequency oscillations (HFOs) (80-500 Hz) were carried out in kainic acid-treated rats with chronic seizures (Bragin et al., 1999a) and in epilepsy patients (Bragin et al., 1999b; Fried et al., 1999). Since then, HFOs have been shown by several centers to be good biomarkers of epileptogenic tissue (Jacobs et al., 2012) and may help to identify the EZ and predict surgical consequences.

Jirsch and co-workers (Jirsch et al., 2006) first recorded HFOs with clinical EEG electrodes (manufactured at the Montreal Neurological Hospital and Institute) and showed an increase of HFOs rates during seizures inside of the SOZ. HFOs were proved to occur reliably in brain tissue generating seizures, thus that they have validity as biomarkers. HFOs were linked to the SOZ (Jacobs et al., 2008; Crepon et al., 2010) and were specific to seizure-generating areas and not to the substrate of pathological tissue in lesional epilepsy (Jacobs et al., 2008).

HFOs can be recorded in interictal episodes, what reduces recording time and consequently risk and discomfort for patients. Interictal HFOs proved to be more specific in localizing the SOZ than spikes (Jacobs et al., 2008) and have shown a good correlation with the post-surgery outcome in epilepsy patients (Jacobs et al., 2010a; Wu et al., 2010; Akiyama et al., 2011; van ’t Klooster et al., 2015).

Wu and co-workers (Wu et al., 2010) actually showed a case where two consequent surgeries were performed. After the first surgery, HFOs remained in one local area, and seizures continued. In the second surgery, all HFO generating area was removed, and patient was completely seizure free. This fact combines evidences towards a strong association between HFOs and epileptogenicity.

However, significant work remains to be done in order for HFOs to fulfill their potential as biomarkers, including identifying strategies to reliably distinguish pathological and physiological HFOs in the human epileptic brain; developing non-invasive methods to record HFOs, which are now best detected using intracerebral EEG recordings; efficient and accurate detection methods and automated tools for unbiased quantification of HFOs in wide bandwidth recordings across patients (Worrell et al., 2012); and, ultimately, prospective studies that can incorporate individual patient HFO data in planning the area for resection and follow patients to determine postsurgical seizure freedom (van ’t Klooster et al., 2015).

1.4 Detection of HFOs

Previously, the analysis of recorded EEG data and detection of HFOs was done manually by a visual inspection. However, this process is very time-consuming and laborious for a viewer (for instance, it takes about 10 hours to visually mark HFOs in a 10-channel 10-min
recording). To avoid that problem recently several automated detection algorithms were proposed. Some of them completely independent and others are still involved an expert observation (Höller et al., 2015). Different tests implemented on a number of randomly chosen patients show that existing methods have been greatly improved during last years and have a good performance (Zelmann et al., 2012; Burnos et al., 2016).

When comparing results from different epilepsy centers, it is important to take into account not only the difference in the optimization of the detector’s algorithms, but also the electrode size, the number and distribution of contacts, the sampling rate, filter settings used and quality of the data. Even a definition of the HFO event could vary between different epilepsy research centers.

The most common definition of the HFO is given by (Jacobs et al., 2012) – spontaneous EEG patterns in the frequency range of 80-500 Hz, consisting of at least four cycles that can be “clearly” distinguished from the background activity (Figure 1.2).

Over the last years, several automated and semi-automated detectors have been proposed. The first automated detector was introduced by Staba et al. (Staba et al., 2002). The root mean square (RMS) amplitude of the filtered (100-500 Hz) signal was computed first. Successive RMS values with amplitude higher a threshold (5 standard deviations above the mean amplitude of the RMS signal), longer than 6 ms in duration were assumed as putative HFOs. The next stage used the number of peaks of the oscillatory event to sort out HFOs from other events with increased amplitude. The EEG was recorded from microwires during period of non-rapid eye movement (NREM) sleep.

In the study of Gardner et al. (2007) the detector was based on the short-time line length. The preprocessing stage included a spectral equalization (first order differential filter), followed by band-pass filtering (30-100 HZ). The threshold was derived from examining the empirical cumulative distribution function of the line length values from a small training set. A human verification was used as the post-processing stage. The
detector was applied for both micro- and macro-electrodes. Lately, the same procedures were implemented on data filtered in the frequency range 80-1000 Hz (Worrell et al., 2008). It was shown that the line length based detector better suited for distinguishing HFOs from background activity than RMS amplitude detector.

A novel approach was introduced by Crepon et al. (2010). Each channel was band-pass filtered (180-320 Hz) and then the envelope of the signal was computed with the Hilbert transform. The event was assumed a putative HFO if it crossed the threshold level (five standard deviations of the envelope over the whole EEG signal). No restrictions on the duration were introduced. Additional visual inspection was done on custom graphical user interface with two band-pass filtered signals and a time-frequency plot using wavelet decomposition (1-400 Hz). The main criteria for selecting HFO events was that the HFO had to be visually detectable on the unfiltered signal as sinusoidal waves and a primary peak on the time-frequency plot had to be in the range 180-400 Hz.

Finally, the detector of Zelmann et al. (2010) used the RMS values of filtered (80-450 Hz) signal. The novel idea was to look at the problem from a perspective similar to how human reviewer marks HFOs manually. Authors used similar procedures as in (Staba et al., 2002; Gardner et al., 2007) in channels with rare HFOs. In channels with continuous high frequency activity an iterative approach was used.

In the study of Zelmann et al. (2012) all different kinds of existing automated detectors were implemented and compared on the same dataset. As a result, authors claimed that a choice of the energy function is almost not relevant, but the approach by which the energy threshold is computed may matter.

In the study of Dümpelmann et al. (2012) a fully automated detector was presented. Three input features were derived from filtered (80-344 Hz) EEG recordings – the short-time energy, short-time line length and short time instantaneous frequency. After training of the parameters of the radial basis function neural network, the detection was implemented. The neural network detector showed much lower accuracy in comparison to semi-automated detectors.

1.5 Outline of the thesis

The main focus of this thesis was 1) to develop new fully automated robust algorithm for detection of HFOs and 2) evaluate the value for the clinical application of the detector for planning epilepsy surgery.

Chapter 2 covers the results published in (Burnos et al., 2014), where we proposed a new method for detection of HFOs that analyzes the instantaneous power spectrum of an individual HFO using the Stockwell Transform. This instrument provides both the real frequency and globally referenced phase measurement characteristics of Fourier transform and also builds local spectra as it does the wavelet transform. The S-transform combines advantages from both algorithms and better results for time-series analysis in comparison to short-time Fourier transform (Stockwell et al., 1996). The detector was evaluated against the SOZ, which serves as the gold standard in the clinical surgical
planning. We proved that the detector was able to detect clinically relevant HFOs, which strongly overlaps with the SOZ.

In Chapter 3, I focus on the problem of separation of HFOs from sharp epileptic spikes. After simulation of events, we proved the existence of two separate classes by principal component analysis and trained a neural network to distinguish HFOs.

Chapter 4 covers the results published in (Burnos et al., 2016), where we further developed the detector and validated it on a visually marked dataset of HFOs, recorded from 30 epilepsy patients in Montreal Neurology Institute. The detector was compared to the existing detectors and evaluated against the SOZ, resected area and post-surgical seizure outcome. Additionally, we proved that HFOs with regular and irregular amplitude similarly reflect the epileptogenicity, and it is not necessary to separate real HFOs from “false oscillations” produced by the filter effect of sharp epileptic spikes (Benar et al., 2010) during visual reviewing or automated detection of HFOs.

In Chapter 5, I present results from (Burnos et al., submitted). We evaluated the automated HFO detector with respect to the post-surgical seizure outcome on patients with epilepsy. We showed that the areas showing high rates of HFOs were associated with the epileptogenic zone. We analyzed the HFO rates with respect to the sites of resection and proved a high value of the automatically detected HFOs for prediction of seizure outcome in individual patients.

Chapter 6 covers the application of the detector in several ongoing projects. The automated detector was applied on the EEG data recorded during surgery from the University Medical Center Utrecht (Fedele et al., 2016) and from the University Hospital Zurich (Fedele et al., submitted). The detector is not limited to the intracranial EEG data, but is applied also to detect HFOs in scalp EEG recordings and in virtual sensors of MEG recordings (van Klink et al., submitted).
Chapter 2. Human intracranial high frequency oscillations detected by automatic time-frequency analysis

This chapter covers the development of the automated detector of HFOs on a set of epilepsy patients. For the detection, the EEG signal was transformed into the time-frequency domain by using the Stockwell Transform. The detector was further evaluated with respect to the seizure onset zone, defined by expert epileptologists during presurgical examinations of the patients.

This work was published in PlosOne (Burnos et al., 2014). I present here the final version of the manuscript prior to publication.

2.1 Abstract

Objectives: High frequency oscillations (HFOs) have been proposed as a new biomarker for epileptogenic tissue. The exact characteristics of clinically relevant HFOs and their detection are still to be defined.

Methods: We propose a new method for HFO detection, which we have applied to six patient iEEGs. In a first stage, events of interest (EoIs) in the iEEG were defined by thresholds of energy and duration. To recognize HFOs among the EoIs, in a second stage the iEEG was Stockwell-transformed into the time-frequency domain, and the instantaneous power spectrum was parameterized. The parameters were optimized for HFO detection in patient 1 and tested in patients 2-5. Channels were ranked by HFO rate and those with rate above half maximum constituted the HFO area. The seizure onset zone (SOZ) served as gold standard.

Results: The detector distinguished HFOs from artifacts and other EEG activity such as interictal epileptiform spikes. Computation took few minutes. We found HFOs with relevant power at frequencies also below the 80-500 Hz band, which is conventionally associated with HFOs. The HFO area overlapped with the SOZ with good specificity > 90% for five patients and one patient was re-operated. The performance of the detector was compared to two well-known detectors.

Conclusions: Compared to methods detecting energy changes in filtered signals, our second stage - analysis in the time-frequency domain - discards spurious detections caused by artifacts or sharp epileptic activity and improves the detection of HFOs. The fast computation and reasonable accuracy hold promise for the diagnostic value of the detector.
Chapter 2. Human intracranial HFOs detected by automatic time-frequency analysis

2.2 Introduction

For patients with epilepsy refractory to medication, neurosurgical resection of the epileptogenic zone is a therapeutic option. As the gold standard in current practice, the epileptogenic zone is approximated by the seizure onset zone (SOZ) defined by presurgical analysis of intracranial EEG (iEEG) (Rosenow and Lüders, 2001). Over the last years, High Frequency Oscillations (HFOs) (Buzsaki et al., 1992) have been evaluated as a new biomarker for the epileptogenic zone (Bragin et al., 1999b; Staba et al., 2004; Urrestarazu et al., 2007; Brázdil et al., 2010; Andrade-Valença et al., 2011; Jacobs et al., 2012; Haegelen et al., 2013). HFOs are defined as spontaneous EEG patterns in the frequency range of 80-500 Hz, consisting of at least four cycles that can be “clearly” distinguished from background noise (Jacobs et al., 2012). HFOs can be recorded during the interictal period and thereby potentially reduce recording time, discomfort and risk for patients. This definition comprises events like ripples (80-250 Hz) and fast ripples (FRs) (250-500 Hz) (Bragin et al., 1999b), but the characteristics of clinically relevant HFOs have not yet been agreed upon.

Since visual marking of HFOs is highly time-consuming, several algorithms for automatic or semi-automatic detection of HFOs have been proposed (Staba et al., 2002; Gardner et al., 2007; Crepon et al., 2010; Zelmann et al., 2010; Akiyama et al., 2011; Dümpelmann et al., 2012; Salami et al., 2012; Birot et al., 2013; Chaibi et al., 2013). While earlier detectors rely rather on thresholds in the time domain, a number of recent detectors also incorporate the frequency domain, which is computationally more demanding.

We propose here the detection of Events of Interest (EoIs) in a first stage of analysis, followed by a second stage that selects HFOs from the set of EoIs. As an extension of the detectors proposed by (Akiyama et al., 2011; Cho et al., 2012; Dümpelmann et al., 2012; Salami et al., 2012; Birot et al., 2013; Chaibi et al., 2013), we analyze the instantaneous power spectral density of an EoI. In order to obtain a precise instantaneous power spectral density, we use the Stockwell transform (Stockwell et al., 1996) that enables an excellent time-frequency decomposition of a signal. The Stockwell transform can be regarded as a generalization of the short-time Fourier transform and a further development of the continuous wavelet transform, combining both advantages (Stockwell, 2007a). Within this signal-processing framework, we can accurately distinguish HFOs, which are short-lived, from long-lived low frequency activity as it may occur during interictal epileptiform spikes (IES). The proposed algorithm has low computational run time and is easy to implement.

We applied the detector to intracranial presurgical diagnostic EEG recordings from six epilepsy patients. We used channels with large numbers of HFOs to identify the epileptogenic zone (Jacobs et al., 2010a; Jacobs et al., 2012; Worrell et al., 2012). We compared this zone to the current gold standard, the SOZ as defined by the clinical presurgical workup based on ictal and interictal activity. In addition, we studied the spectral frequency of individual HFOs.
2.3 Methods

2.3.1 Patient selection

We included all patients that were implanted with intracranial electrodes at the Neurosurgery Department from March 2012 to March 2013 and where iEEG could be recorded with a sampling frequency of at least 2000 Hz. This selection criterion resulted in six patients (all male, median age 25 years). Patient characteristics and implantation sites are given in Table 2.1.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Age at</th>
<th>MRI</th>
<th>Histology</th>
<th>Number of implanted electrodes</th>
<th>Implantation sites</th>
<th>Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>21</td>
<td>2</td>
<td>HS (left MTL)</td>
<td>HS type 1a</td>
<td>8</td>
<td>AL, ECL, HL, PCL, AR, ECR, HR, PCR</td>
<td>sAHE</td>
</tr>
<tr>
<td>2</td>
<td>21</td>
<td>3</td>
<td>HS (left MTL) &amp; right frontal FCD</td>
<td>-</td>
<td>7</td>
<td>AL, ECL, HL, PH, ECR, HR, PCR</td>
<td>DBS</td>
</tr>
<tr>
<td>3</td>
<td>34</td>
<td>25</td>
<td>bilateral HS</td>
<td>-</td>
<td>5</td>
<td>ECL, HL AR, ECR, HR</td>
<td>DBS</td>
</tr>
<tr>
<td>4</td>
<td>48</td>
<td>2</td>
<td>HS (left MTL)</td>
<td>HS (no classification)</td>
<td>8</td>
<td>AL, ECL, HL, PCL, AR, ECR, HR, PCR</td>
<td>sAHE</td>
</tr>
<tr>
<td>5</td>
<td>27</td>
<td>1</td>
<td>right frontal FCD</td>
<td>FCD type 2a</td>
<td>3</td>
<td>FAR, TR, FPR</td>
<td>LE</td>
</tr>
<tr>
<td>6</td>
<td>22</td>
<td>11</td>
<td>no lesion</td>
<td>-</td>
<td>5</td>
<td>TLL, TBAL, TBPL, TBAL, TBPR</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 2.1 Clinical data and implantation sites. Pathologies: FCD focal cortical dysplasia; HS hippocampal sclerosis. Procedures: DBS deep brain stimulation; LE extended lesionectomy; sAHE selective amygdala-hippocampectomy. Implantation sites: AL amygdala left; AR amygdala right; EL entorhinal cortex left; ER entorhinal cortex right; FAR frontal anterior right; FL frontal lobe; FPR frontal posterior right; HL hippocampus left; HR hippocampus right; MTL mesial temporal lobe; PL perirhinal cortex left; PR perirhinal cortex right; TBAL temporal basal anterior left; TBAR temporal basal anterior right; TBPL temporal basal posterior left; TBPR temporal basal posterior right; TR depth frontal right; TLL temporal lateral left.

2.3.2 Ethics statement

Collection of personal patient data and retrospective scientific workup was approved by the institutional ethics review board (Kantonale Ethikkommission KEK-ZH-Nr. 2012-0212) and collection of patients’ written informed consent was waived.
2.3.3 Electrode types and implantation sites

Intracranial depth macro electrodes and subdural strips and grids were implanted at locations planned according to the results of the previous non-invasive presurgical workup.

Mesiotemporal depth electrodes (1.3 mm diameter, 8 contacts of 1.6 mm length, spacing between contacts 5 mm, ADTech, www.adtechmedical.com) were implanted stereotactically into the amygdala, the hippocampal head and the entorhinal and perirhinal cortex bilaterally.

For cortical sites, a combination of depth and subdural strip and grid electrodes (contact diameter 4 mm with a 2.3 mm exposure, spacing between contact centers 10 mm) was placed after craniotomy. Here depth electrodes were implanted into the supposed center of bottom-of-sulcus dysplasias as defined by morphometric postprocessing of MR images (Wellmer et al., 2010).

An image-guidance system was used (StealthStation, Medtronic, www.medtronic.com). Pre- and post-implantation magnetic-resonance imaging (MRI) and computer tomography (CT) scans were used to locate each contact anatomically along the electrode trajectory.

2.3.4 Data acquisition

Data was recorded for presurgical evaluation starting from the day after electrode implantation. The recording was performed in the intensive monitoring unit under video surveillance at the Swiss Epilepsy Centre. Intracranial data was acquired at 4000 Hz with an ATLAS recording system (Neuralynx, www.neuralynx.com) and downsampled to 2000 Hz for HFO analysis. In addition, surface EEG and the submental electromyogram (EMG) were recorded. Intracranial data was recorded against a common reference and then transformed to a bipolar montage for further analysis.

2.3.5 Data selection

We selected interictal samples of five minutes of slow-wave sleep because of reduced muscle activity and because HFOs occur more often during slow-wave sleep than during wakefulness (Staba et al., 2004; Clemens et al., 2007). Sleep staging was performed based on scalp EEG, electrooculogram (EOG), EMG and video recordings. The selected data samples were separated from epileptic seizures by at least three hours to reduce the influence of seizures on our analysis.

2.3.6 Data analysis

The aim of our detector was to distinguish HFOs from other iEEG activity and artifacts. In this paragraph, we present the rationale of the detector and we present details in the following sections. Our HFO detector involves two stages. In the first stage, after pre-
filtering the signal, possible events of interest (EoIs) were detected based on thresholds in the time domain. This signal processing stage was optimized to ensure a high sensitivity and we accepted a low specificity to obtain a large number of EoIs. In the second stage, we reviewed all EoIs in the time-frequency domain in order to recognize HFOs. Following the recommendation in (Jacobs et al., 2010a), this was first done by visual inspection in separate windows as in Figure 2.1 for up to 10 channels simultaneously. In addition, both stages of HFO detection were performed automatically with custom scripts written in MATLAB (www.mathworks.com).

2.3.7 Stage 1: Detection of EoIs

First, the signal was band-pass filtered from 80 to 500 Hz. We used an Infinite Impulse Response (IIR) Cauer filter, 60 dB minimum lower/upper stop band attenuation, 0.5 dB maximum pass band ripple, 10 Hz lower/upper transition width, forward and reverse filtered in order to avoid phase distortion. To ensure filter stability we performed extensive testing with the MATLAB filter design toolbox. While other groups use FIR filters (Staba et al., 2002; Zelmann et al., 2009; Crepon et al., 2010), we prefer IIR filters because IIR filters reduce computational run time 100-fold in our algorithm and have a sharp cut-off as well as a narrow transition width. Figure 2.1 shows a typical raw signal (panels A and B), which was then band-passed (panel C).

We then scanned the signal for events of high amplitude and sufficient duration to qualify as EoIs. The detection of EoIs proceeded in the following steps (Staba et al., 2002).

1. We calculated an envelope of the band-passed signal using the Hilbert transformation (Crepon et al., 2010; Kalitzin et al., 2012).
2. We calculated the standard deviation (SD) of the envelope of the 5 min of data. We then set a threshold at the mean of the envelope plus 3 SD.
3. An event was marked when the envelope exceeded the threshold. The duration of the event was defined as the interval between upward and downward crossing of 0.5*threshold. If its duration exceeded 6 ms, this event qualified as an EoI.
4. We merged EoIs with an inter-event-interval of less than 10 ms into one EoI.
5. Events not having a minimum of 6 peaks (band-passed signal rectified above 0 μV) greater than 2 SD from the mean baseline signal were rejected (Staba et al., 2002).

2.3.8 Stage 2: Recognition of HFOs among EoIs

In the second stage, we distinguished HFOs from EoIs that were elicited by other EEG activity and artifacts (Otsubo et al., 2008; Zijlmans et al., 2012b). We implicitly assume that an HFO appears as a short-lived event with an isolated spectral peak at a distinct frequency (Crepon et al., 2010; Cho et al., 2012). We therefore reviewed all EoIs and transformed the period of [-0.5 s, +0.5 s] into time-frequency space.
For this transformation we used the Stockwell transform (Stockwell et al., 1996) because it yields superior peak sharpness compared to the short-time Fourier Transform at similar computational speed for our time series of 1 s. In both cases, the frequency resolution is 1 Hz. Compared to the short-time Fourier transform, the Stockwell transform does not use a window with a constant width but relies on a frequency dependent window width, which increases the time-frequency resolution. Thus, the Stockwell transform is a hybrid of the short-time Fourier transform and the continuous wavelet transform, combining the advantages of both methods (Stockwell et al., 1996; Stockwell, 2007b; Assous and Boashash, 2012).

**Figure 2.1 HFO in a temporomesial recording.** (A) Raw iEEG 10 s epoch from channel HL1 in patient 1. (B) Raw iEEG at extended time scale of 500 ms. (C) Filtered iEEG of panel B with envelope (red line). The envelope satisfies the criteria for an EoI (Stage 1 of detection). The peak of the envelope is marked by dashed vertical lines in panels A, B and C. (D) Time frequency representation of the iEEG of panel B. The circle marks the peak of the envelope of the EoI. The “blob” represents the HFO. (E) Power spectral density (PSD, unit: \(10\log_{10}\mu\text{V}^2\text{Hz}^{-1}\)) at the peak of the EoI. For the event illustrated here, there is an HFO peak at 116 Hz, a trough at 73 Hz and a low frequency peak at 47 Hz. The thin line shows the PSD of the same data calculated by the short-time Fast Fourier Transform for comparison.
Figure 2.1D shows an EoI in time-frequency space. Only a period of 0.5 s around the EoI is displayed to mask boundary effects. To qualify as an HFO, the EoI must exhibit a high frequency peak, which is isolated from low frequency activity by a spectral trough. To recognize HFOs automatically, we analyzed the instantaneous power spectra of the TF representation (Figure 2.1E, PSD unit: 10log10µV^2Hz^{-1}) around the maximum of the envelope (vertical dashed line in Figure 2.1C). The instantaneous power spectra were computed for all time points of the envelope within the full width at half maximum above the threshold (FWHM). This boundary assures that the maximum of the envelope and its neighborhood above the threshold is taken into analysis. The instantaneous power spectrum for each time point was parameterized by three frequency bins in the following way.

**Figure 2.2 Sharp artifact.** (A) Raw iEEG data 10 s epoch from a frontal channel in patient 6. (B) Raw iEEG at extended time scale. (C) Filtered data (blue line) with envelope (red line). The envelope satisfies the criteria for an EoI (Stage 1 of detection). While the high-frequency activity is separated by a trough (D, E), it is excluded from acceptance as HFO because the peak of the spectral power appears at frequencies above 500Hz.
1. We selected the high frequency peak (HiFP) as the spectral peak of a putative HFO. This HiFP was selected in the spectral range from $f_{\text{min}}$\text{(HiFP)} = 60 Hz to 500 Hz. The lower edge (60 Hz) was chosen heuristically to avoid 50 Hz line hum in the signal.

2. We defined the trough as the minimum in the range between $f_{\text{min}}$\text{(trough)} = 40 Hz and the HiFP.

3. We defined the low frequency peak (LoFP) as the closest local maximum below the trough.

These three frequency bins were used to distinguish HFOs in the instantaneous spectrum at each time point within the FWHM. To qualify as an HFO, we demand a trough of sufficient depth $\text{Power(Trough)} / \text{Power(HiFP)} < 0.8$ and a HiFP peak of sufficient height $\text{Power(HiFP)} / \text{Power(LoFP)} > R_{\text{thr}} = 0.5$. These two conditions have to be satisfied by all instantaneous power spectra within the FWHM.

For further analysis, we defined the high frequency peak, the trough and the low frequency peak of an individual HFO as the HiFP, trough and LoFP at the time point when the envelope reaches its peak.

Figure 2.2 shows a short sharp artifact, which qualified as an EoI in Stage 1 of the analysis. It was excluded from acceptance as an HFO because the peak of the spectral power appeared at frequencies above 500 Hz (Figure 2.2E).

2.3.9 Definition of the SOZ

In all patients presented here, the surgical planning of the resection area was based on the SOZ, which we take as the gold standard. In conventional analysis of clinical EEG recordings, epileptic seizures are reviewed visually. The channels with the earliest signs of ictal EEG activity define the SOZ (Kral et al., 2002). It is usually necessary though not sufficient to resect the SOZ as part of the epileptogenic zone, which in turn is defined as the area that has to be resected to achieve seizure freedom. In most cases, the epileptogenic zone also includes the epileptogenic lesion (if present and removable) and adjacent regions of consistent early spread of seizure activity. In addition, epileptiform potentials like IES or “spike-waves” are reviewed to delineate irritative zones of cortex against healthy tissue.

2.3.10 Separate data sets for training and testing the detector

To optimize parameters for HFO detection, we selected the data from patient 1 as the training set. In this patient, the SOZ contained only two channels (HL1-HL2, HL2-HL3; Table 2.2). We assumed that these channels indicate the epileptogenic zone (Rosenow and Lüders, 2001) and therefore optimized parameters for detection of these channels. To test the performance of the detector, we selected patients 2-6 as the test set.
2.3.11 Definition of the HFO area

We computed the rates of automatically detected HFOs in the 5 min data sample. We analyzed the spatial distribution of HFOs rates for each patient by ranking channels by their HFO rate. The width of distribution was captured by its half maximum. The channels with HFO rate higher than the half maximum constitute the HFO area, which we assume to indicate the location of the epileptogenic zone.
In addition to the half maximum threshold, we also tried Kittler’s method to separate channels with high HFO rates (Kittler and Illingworth, 1986). The results for sensitivity and specificity were similar to within a few percent points so that the data are not shown here.

2.3.12 Statistical analysis

The channels within the HFO area were counted as true positives (TP) if they were located within the SOZ and were counted as false positives (FP) if they were located outside of the SOZ. The channels outside of the HFO area were counted as false negatives (FN) if they were located within the SOZ and were counted as true negatives (TN) if they were located outside of the SOZ. The sensitivity was calculated as sens = TP/(TP + FN), the false-positive rate as FPR = FP/(FP + TN) and the specificity as spec = 1 – FPR. 95% confidence intervals (CI) were estimated based on the binomial distribution. We use the values of the sensitivity and the specificity to quantify the performance of our detector in the sense of how strongly the HFO area overlaps with the SOZ.
2.4 Results

2.4.1 Examples of EoIs and HFOs in individual patients

Figure 2.1 shows an example of an HFO recorded from the hippocampal channel HL1 of patient 1. The HFO appears as a short-lived event that is clearly distinct from low-frequency activity (Figure 2.1D).

The IES shown in Figure 2.3 also appears as a short-lived event in the band-passed
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channel (Figure 2.3C) and qualifies as an EoI in Stage 1 of our analysis. The EoI is not accepted as an HFO in Stage 2 of the analysis because the event shows a smooth transition between high and low frequency activity in the absence of a trough.

Figure 2.4 depicts an EoI that appeared as an HFO in visual inspection. Energy and duration of the event met the Stage 1 requirements of an EoI. However, its high frequency peak is at 60 Hz, which is lower than common definition of HFOs (>80 Hz). Therefore, in the Stage 2, we limited the lowest boundary for HiFP at 60 Hz and this EoI was accepted as an HFO by our detector.

Figure 2.4 HFO with frequency peak below 80 Hz. (A) Raw iEEG data 10 s epoch from channel HL6 in patient 1. (B) Raw iEEG at extended time scale of 500 ms. (C) Filtered iEEG with envelope (red line). The envelope satisfies the criteria for an EoI (Stage 1 of detection). The EoI is salient enough to be separated from low-frequency activity by a trough (D, E). This EoI has the visual appearance of an HFO but the peak frequency is around 60 Hz. Therefore, in Stage 2 the lowest boundary for a HiFP was chosen at 60 Hz and this EoI was accepted as HFO by our detector.
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An HFO from a neocortical recording in patient 6 is shown in Figure 2.5. The HFO appears less salient than in temporomesial recordings.

Figure 2.5 HFO in a neocortical recording. (A) Raw iEEG data 10 s epoch recorded from a frontal channel in patient 6. (B) Raw iEEG at extended time scale of 500 ms. (C) Filtered data with envelope (red line). The envelope satisfies the criteria for an EoI. The peak of the envelope is marked by dashed vertical lines in panels A, B and C. (D) Time frequency representation of the iEEG of panel B. The circle marks the peak of the envelope of the EoI. (E) Power spectral density (PSD, unit: 10log[µV²Hz⁻¹]) at the peak of the envelope. The high frequency peak is at 82 Hz, the trough at 40 Hz and the low frequency peak at 30 Hz for this event, which was accepted as HFO in Stage 2 of the detection.

2.4.2 Characteristics of HFOs in individual patients

Table 2.3 presents the total number of EoIs and HFOs that were detected in each individual patient. The mean characteristics of HFOs are all in the same range for both temporomesial implantation sites (patients 1, 2, 3 and 4) and neocortical implantation sites (patients 5 and 6). Among all EoIs detected in stage 1, an average 66% of events were
accepted as HFOs. Patient 4 showed the lowest acceptance rate 32%, and patient 5 and 6 had the highest rates 83% and 79% respectively. Furthermore, our algorithm allowed us to detect HFOs with widely varying duration (Table 2.3).

<table>
<thead>
<tr>
<th>Patient</th>
<th>Channels</th>
<th>EoIs</th>
<th>HFOs</th>
<th>Acceptance rate [%]</th>
<th>Ripples / FRs</th>
<th>HFO rate per channel, mean±SD [1/min]</th>
<th>HFO duration, mean±SD [ms]</th>
<th>HFO peak, mean±SD [Hz]</th>
<th>Trough frequency, mean±SD [Hz]</th>
<th>Low frequency peak, mean±SD [Hz]</th>
<th>Amplitude, mean±SD [µV]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>56</td>
<td>796</td>
<td>378</td>
<td>47%</td>
<td>337/41</td>
<td>7 ± 11</td>
<td>58 ± 34</td>
<td>113 ± 55</td>
<td>58 ± 20</td>
<td>39 ± 18</td>
<td>16 ± 26</td>
</tr>
<tr>
<td>2</td>
<td>49</td>
<td>245</td>
<td>91</td>
<td>37%</td>
<td>77/14</td>
<td>2 ± 4</td>
<td>47 ± 26</td>
<td>141 ± 78</td>
<td>57 ± 19</td>
<td>39 ± 17</td>
<td>77 ± 114</td>
</tr>
<tr>
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<td>35</td>
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<td>387</td>
<td>44%</td>
<td>292/95</td>
<td>11 ± 23</td>
<td>41 ± 15</td>
<td>159 ± 90</td>
<td>71 ± 33</td>
<td>42 ± 26</td>
<td>57 ± 40</td>
</tr>
<tr>
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<td>56</td>
<td>1013</td>
<td>323</td>
<td>32%</td>
<td>317/6</td>
<td>1 ± 9</td>
<td>58 ± 25</td>
<td>93 ± 30</td>
<td>56 ± 16</td>
<td>38 ± 13</td>
<td>20 ± 22</td>
</tr>
<tr>
<td>5</td>
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<td>3724</td>
<td>3104</td>
<td>83%</td>
<td>3104/0</td>
<td>80 ± 29</td>
<td>91 ± 48</td>
<td>94 ± 16</td>
<td>52 ± 11</td>
<td>37 ± 12</td>
<td>82 ± 61</td>
</tr>
<tr>
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<td>457</td>
<td>79%</td>
<td>457/0</td>
<td>13 ± 19</td>
<td>67 ± 48</td>
<td>82 ± 16</td>
<td>51 ± 11</td>
<td>37 ± 10</td>
<td>21 ± 11</td>
</tr>
</tbody>
</table>

Table 2.3 Temporal and spectral characteristics of HFOs in individual patients. For each patient we present the total number of EoIs detected in Stage 1 and the number of HFOs accepted in Stage 2. Based on their peak frequency, HFOs were then classified into ripples (80-200 Hz) and fast ripples (FRs, 200-500 Hz).

We classified HFOs by their high frequency peak into ripples (80-200 Hz) and FRs (200-500 Hz) and presented the respective rates as a column in Table 2.3. In our patient group, we observed a predominance of ripples over FRs. This predominance may be accentuated by our classification method, which classifies an HFO as a ripple even if an FR occurs simultaneously. Figure 2.6 represents an example of correctly identified FR.

Figure 2.7 shows the channel count as a function of HFO rate in each individual patient. The HFO area is given in Table 2.2 in terms of absolute number of channels and also normalized by the total number of channels. The spatial distributions of HFOs in patients 1, 2, 3, 4 and 6 are focused on a few channels. Widespread occurrence of HFOs as in patient 5 suggests a widespread epileptogenic zone.

As an advantage of our HFO-detection in the time-frequency domain, we can determine the peak frequency for each individual HFO. Figure 2.8 shows the distribution of peak frequencies for medial temporal and neocortical recordings separately. The peaks of HFOs from temporomesial recordings are more widely distributed in frequency than those from neocortical recordings. Furthermore, 22% of temporomesial and also 22% of neocortical HFOs exhibit maxima below 80Hz.
2.4.3 Comparison with the clinical delineation of the SOZ

Channels with HFO rates ≥ half maximum are listed in Table 2.2 for all six patients. HFO channels corresponded to the location of the SOZ to a varying degree.

In patient 1, the SOZ were found in left temporomesial channels (HL1, HL2) and a left-sided selective amygdala-hippocampectomy was performed. The three channels with the highest HFO rate were also in the left hemisphere (HL1, PL1, and PL2). There were 3 channels with markedly lower HFO rates but still within the HFO area (HL6, ER1, ER2) that are counted as FP, resulting in spec = 91% CI [80-97%]. Channel HL2 from the SOZ showed
an HFO rate below the half maximum resulting in sens = 50% CI [13-99%]. Visual inspection as a complement to automatic HFO detection did not reveal additional HFOs in this channel.

Figure 2.7 Channels ranked by HFO rate. Channels with high HFO rate are assumed to mark the epileptogenic zone. Channels with HFO rate above the half maximum (black bars) constitute the HFO area. The channel locations of the HFO area in each patient is given in Table 2.3.

Figure 2.8 HFO peak frequency distribution. (A) Total of all HFOs recorded from the four patients with temporomesial electrodes (N=1179). The sharp edge to low frequencies stems from the frequency threshold of 60 Hz of the detector. (B) Total of all HFOs recorded from the two patients with neocortical electrodes (N=3561). The distributions are fitted with a lognormal function (red line). The frequency peaks of HFOs from temporomesial recordings are more widely distributed than those from neocortical recordings.
In patient 2, HFOs were found bilaterally in temporomesial channels in agreement with the SOZ, which was also found bilaterally. The individual channels were not the same, which results in only one TP and a low sens = 14% CI [4-58%]. Channels outside of the SOZ did not show HFOs, resulting in an adequate spec = 95% CI [84-99%]. Based on the location of the SOZ, the therapeutic decision was not to resect but to offer deep brain stimulation (DBS) to this patient. HFO analysis would have led to the same therapeutic decision.

In patient 3, the HFO area closely overlapped with the SOZ as shown by the high values of sens = 75% CI [20-99%] and spec = 94% CI [79-99%]. Again, the SOZ was bilateral so that DBS was offered also to this patient.

In patient 4, the SOZ and HFOs were found in left temporomesial channels and a left-sided selective amygdala-hippocampectomy was performed. In addition, HFOs were found in one right-sided channel, resulting in sens = 75% CI [20-99%] and spec = 94% CI [84-99%].

In patient 5, all but one channel of the SOZ were found within the HFO area resulting in sens = 94% CI [70-100%]. In addition, there were 14 false positive HFO channels, so that spec = 39% CI [20-61%]. An extended lesionectomy was performed in this patient. However, the postsurgical outcome was poor, so that the patient was operated on for a second time, which resulted in a more than 90% reduction of seizure frequency though not in complete seizure freedom. Thus, the low spec = 39% may be a consequence of the unsuccessful delineation of the SOZ.

In patient 6, the SOZ extended over 15 of 36 channels. High HFO rates occurred in a large number of channels and an exceptionally high rate in two channels. Only these two channels constituted the HFO area, resulting in a high spec = 100% CI [86-100%] but a low sens = 13% CI [2-40%]. Surgery on this patient was postponed for clinical reasons.

Taken together, over the group of 6 patients the sensitivity was ≥ 75% in 3 patients. Specificity exceeded 90% in all but the one patient who was re-operated.

2.4.4 Sensitivity analysis

To motivate the choice of parameters, we tested how the sensitivity and specificity values were influenced by the energy threshold in Stage 1 of our detector on our training data set (Patient 1). Changing the threshold to 2 SD increased the maximum HFO rate to 15 /min. However, the ranking of channels was fairly robust with respect to parameter-variations in the detector, because thresholds for EoIs are defined with respect to the variance of the data, and the recognition of HFOs depends on relative spectral properties. The combination of sensitivity/specificity for detection of the SOZ was sens = 50% CI [13-99%] and spec = 91% CI [80-97%] for thresholds of 2 SD, 2.5 SD, 3 and 4 SD. Only at 1 SD was the maximum HFO rate 30 1/min but the enhanced number of false positive HFOs and false positive HFO channels reduced specificity to 81% CI [69-91%].

2.4.5 Comparison to existing detectors

We compared the performance of our detector with two automatic detectors that are well established in literature. The first one was proposed by (Staba et al., 2002), we will refer to
this detector as RMS detector. The second one was proposed by (Gardner et al., 2007), we will refer to this detector as LineLength detector.

RMS detector is based on the energy defined as the moving average of the root mean square (RMS; 3-ms sliding window) amplitude of the filtered signal. Each channel was first band-pass filtered (100-500 Hz). Then segments with energy above five times the SD of the mean energy of the whole EEG during more than 6 ms were defined as HFOs. Consecutive events separated by less than 10 ms were combined as one event. Events not having a minimum of 6 peaks (band-passed signal rectified above 0 µV) greater than 3 SD from the mean baseline signal were rejected.

In LineLength detector, the short-time energy was replaced by short-time line length. The short-time line length is assumed to be less sensitive against outliers than the short-time energy. First, each channel was band-pass filtered (80-500 Hz). Then, segments with energy above five times the SD of the mean energy of the whole EEG during more than 6 ms were defined as HFOs. Consecutive events separated by less than 10 ms were combined to one event.

To benchmark RMS detector, LineLength detector and our detector with the SOZ, we then defined the HFO area by the half maximum method (section “Definition of the HFO area”). For all three detectors, the sensitivity and specificity for HFO channels to mark the SOZ is presented in Table 2.4. The sensitivity and the specificity were equal in 2 patients and considerably lower for RMS and LineLength detectors in 4 patients.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Our detector</th>
<th>RMS detector</th>
<th>LineLength detector</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sens [%]</td>
<td>Cl [%]</td>
<td>Spec [%]</td>
</tr>
<tr>
<td>1</td>
<td>50</td>
<td>13-99</td>
<td>91</td>
</tr>
<tr>
<td>2</td>
<td>14</td>
<td>0-64</td>
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<td>3</td>
<td>75</td>
<td>19-99</td>
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<tr>
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<td>94</td>
<td>70-100</td>
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</tr>
<tr>
<td>6</td>
<td>13</td>
<td>2-40</td>
<td>100</td>
</tr>
</tbody>
</table>

Table 2.4 Comparison to existing detectors. We defined the HFO area by the half maximum method for all three detectors. Sens – sensitivity, spec – specificity and CI – confidence intervals as defined in Section 2.3.12.

2.4.6 Computational aspects

We implemented the algorithm on a PC with a 64-bit operating system (Windows XP), and 8 GB RAM and 3.40 GHz CPU. For 5 minutes of recording of 50 channels with 4 KHz sampling rate the size of a file is about 60 Mbit. The computational run time for the Stage 1 (detection of EoIs) depended mainly on the choice of filters for band-pass filtering of the raw signal. Run time is dramatically decreased when using IIR filter instead of FIR family filters. For 5 min of data in a single channel, Stage 1 took 2 sec of CPU time.
Chapter 2. Human intracranial HFOs detected by automatic time-frequency analysis

The time needed in Stage 2 of the computational process depends mainly on the number of EoIs that have to be reviewed and the type of time-frequency transform. We have compared the Stockwell Transform, which was implemented in our detector, with the short-time Fourier Transform. For the 1 sec data-epoch that an EoI is reviewed, both transforms were equally fast. Recognition of an individual HFO consumes 140ms of CPU time in our setting. However, the Stockwell Transform turned out to be superior to the short time Fourier Transform with respect to the sharpness needed for HFO recognition in the instantaneous power spectrum (Figure 2.1E).

2.5 Discussion

2.5.1 Reliability of detection of the epileptogenic zone

We present here a newly developed detector for HFOs in the time-frequency domain. The final goal of the detector is to aid in rapid identification of the epileptogenic zone in order to aid in planning the surgical resection. The only proof that the epileptogenic zone has been resected is postoperative seizure freedom. In addition, healthy parts of the brain may have been resected. Because of the small number of patients and because three of the patients did not undergo surgical resection, our gold standard to approximate the epileptogenic zone is the SOZ, which was defined during presurgical workup. The SOZ provides the basis for clinical decisions. However, the definition of the SOZ may also be flawed, as can be the case in patient 5 who did not become seizure-free postoperatively and had to be re-operated on. In this patient, the HFO area exceeded the SOZ and therefore HFOs may be more sensitive markers of the epileptogenic zone.

To judge the reliability of any HFO-detector, the following assumptions must be kept in mind. 1) Based on the literature, we assume that a high rate of pathological HFOs is a reliable marker of the epileptogenic zone (Jacobs et al., 2009; Jacobs et al., 2010b; Akiyama et al., 2011; Zijlmans et al., 2012b; Haegelen et al., 2013). We assume this is also the case for patients with very different types of epilepsy. 2) However, there is not yet a decisive consensus on the exact characteristics of clinically relevant HFOs, i.e. the distinction between pathological and physiological HFOs remains uncertain (Zelmann et al., 2012). We assume that our detector distinguishes pathological HFOs from artifacts and other EEG activity. We validated all detected events by visual inspection to establish their quality and veracity. 3) We distinguish between channels within or outside the HFO area and by setting a threshold in HFO rate. Other authors have used a similar approach (e.g. (Urrestarazu et al., 2007; Jacobs et al., 2010a)). A more elaborate approach with Kittler’s method (Kittler and Illingworth, 1986; Akiyama et al., 2011) did not yield superior sensitivity in our data so that we propose the half maximum threshold as a simple algorithm to determine this threshold. All three of these assumptions affect the reliability of a detector.

The delineation of the SOZ is done on a channel-by-channel basis, but surgical decisions are taken in a wider context. For example, if epilepsy surgery is to be performed in form of
a selective amygdala-hippocampectomy (sAHE), standard resection includes the amygdala, the anterior hippocampus proper and parts of the parahippocampal gyrus, including the entorhinal and perirhinal cortices, at least in part. If seizure recordings have lateralized the SOZ to one side and localized it within the hippocampus by recording the seizure onset with the first two contacts of a hippocampal depth electrode (HL1 and HL2 in patient 1), it does not matter whether HFOs can be found in contact HL1, or HL2, or both of them: Both channels are usually situated within the hippocampus proper, and thus identify the same structure to be resected. Thus, our test of the HFO area against the SOZ on a channel-by-channel basis is very rigorous and leads to low values of sensitivity down to 13% (Table 2.3). We have chosen this test criterion because it is straightforward and common practice (e.g. (Jacobs et al., 2010a)). A test criterion could also be based on the types of neurosurgical resection that are standard procedures in epilepsy surgery. For such a criterion, the sensitivity of our HFO detector would be higher.

2.5.2 Spectral frequency of HFOs

In view of the good performance of our detector, we refrained from distinguishing HFO events into ripples and FRs, even though other authors adhere to this distinction, e.g. (Staba et al., 2002; Crepon et al., 2010; Jacobs et al., 2010a).

Our detector encountered events that feature their maximal power spectral density below 80 Hz. An example is depicted in Figure 2.4. The asymmetric distribution of HFO spectral maxima in Figure 2.8B suggests that HFOs may exhibit maxima even below 80 Hz. There were events, which met the requirements of EoIs, but were not recognized as HFOs because of our frequency cutoff at 60 Hz. This finding shows that the lower edge of the HFO-band is critical for HFO detection. The frequency of HFOs below 80 Hz overlaps with what is conventionally termed the gamma band (Worrell et al., 2012).

2.5.3 Relation between HFO and IES

It is well known that HFOs can occur simultaneously with IES (Urrestarazu et al., 2007). By averaging over a set of 50 HFOs time-locked to an IES, it was shown that HFOs occur at frequencies distinct from those of the IES in a time-frequency plot (Kobayashi et al., 2010). We can reproduce this finding for individual HFOs without the need for averaging and without the need of time locking to an IES (see Figure 1.3 for an example).

2.5.4 Advantages of the two stages of detection

We aim to distinguish HFO events from other EEG activity and artifacts. Our HFO detector involves two stages. In the first stage, possible events of interest (EoIs) are detected based on thresholds in the time domain. The sensitivity analysis for the energy threshold in our test set was presented in Section 2.4.4. In this stage of HFO detection, we emphasize sensitivity to obtain a large number of EoIs. However, high pass filtering of sharp events
like IES or artifacts may cause filter ringing that is sufficiently large to be detected as “false ripples” (Benar et al., 2010).

In order to discard such events and to limit detection to distinct HFOs, we subsequently review all EoIs in the time-frequency domain. In Stage 2, our detector analyses not a fixed time window but only those time points where the high-frequency activity is above the FWHM. This enables us to look at the microstructure of the event. Conceptually this is different from methods that average over time. We computed a set of instantaneous power spectra in a time window of 1 sec. Our method relies on instantaneous power spectra as they can only be obtained by a time-frequency (TF) analysis. In our detector, no window length has to be fixed for the TF-transformation. Making use of the high time resolution, we analyzed several instantaneous spectra (5 to 50) around the Hilbert peak of each event. This detection algorithm is based on the instantaneous power spectral estimation, which periodograms or autoregressive models cannot provide at this high temporal resolution. The power spectra of this subset were not averaged either over time or over frequency, but each instantaneous power spectrum was tested with the criterion for HFO acceptance. Stage 2 of the detector thus emphasizes specificity.

The combination of these two stages provides good accuracy for detection of HFOs in human iEEG recordings.

2.5.5 Comparison to existing detectors

The detection of EoI in Stage 1 of our detector was programmed along the lines of algorithms proposed by (Staba et al., 2002) and (Crepon et al., 2010). For testing purposes, we implemented RMS and LineLength detectors (see Section 2.4.5). For both detectors, the sensitivity and specificity for HFO channels was equal in 2 patients and considerably lower in 4 patients than in our detector.

The detector of (Cho et al., 2012) is, like our Stage 1, also derived from (Crepon et al., 2010). It first detects events in the time domain and then uses wavelet-based time-frequency decomposition to validate detected events visually. We went further and used the time-frequency analysis for automatic validation of detected EoIs.

Recently, a set of detectors has been described, which also detect EoIs in a first stage and then automatically recognize HFOs in a second stage in the time-frequency domain. After either Fourier Transform or Wavelet Transform, the detector proposed by (Birot et al., 2013) was shown to detect FRs in the frequency band 256-512 Hz. The choice of frequency band is restricted by decomposition levels of the dyadic wavelet transform. This method computes energy ratios in different frequency levels and has a good spectral resolution for signals in the FR frequency range. The Time-Frequency Transform by Stockwell extends the ideas of the wavelet transform such that decomposition levels can be adjusted according to the aim of detection. As a further advantage, it is based on the true frequency spectrum and globally referenced phase measurements like the Fourier transform.

The time-frequency characteristics of individual HFOs can be clearly described due to the good time-frequency resolution of the Stockwell Transform. This is an advantage over
automatic or visual detection of HFOs based on data high-pass filtered at 80 Hz (Jacobs et al., 2012; Zijlmans et al., 2012b). While we also high-pass filter at 80 Hz in Stage 1 of our detector, we analyze the complete raw iEEG in Stage 2 where we review EoIs to detect HFOs.

### 2.5.6 Limitations of the study

The thresholds of the detector were trained heuristically to optimize sensitivity/specificity in patient 1 (see Section 1.4.4). While the thresholds were kept constant for all patients in the test set, the performance of the detector should be tested with a larger group of patients.

There were events, which met the requirements of EoIs, but were not recognized as HFOs because of the frequency restriction for HFO selection. To cope with line hum, our detector is limited to events with maximal power spectral density above 60 Hz.

Furthermore, the performance is compared to the definition of the SOZ, which is the gold standard for definition of the resection margin. However, the performance of the detector should be evaluated against clinical outcome, which is beyond the scope of the current study.

### 2.5.7 Outlook on possible clinical relevance of the detector

At its current stage of development, the detector is judged against the gold standard of the SOZ as defined by an experienced epileptologist. This is justified because the characteristics of a clinically relevant HFO are still not agreed on. Eventually the clinical relevance of the HFOs detected here should be tested against the outcome after surgery. The fact that HFOs occurred with several pathologies (Table 2.1) is consistent with the idea that HFOs are a biomarker of the epileptogenic zone, regardless of seizure etiology (Jacobs et al., 2010a).

All the necessary information for HFO analysis was obtained from 5 minutes of interictal data recorded during deep sleep, at least 3 hours separated from a seizure. Contrarily, the current gold standard of presurgical diagnostics requires the recording of several epileptic seizures to delineate the SOZ. In this way, HFO analysis can potentially reduce recording time and patient risk as it may occur due to delayed epilepsy surgery.

As an advantage, the low computational run time of the algorithm enables an online implementation of the detector. This could permit application of the detector in an intraoperative setting (Wu et al., 2010; Zijlmans et al., 2012a). The detector might then become a supplementary diagnostic tool for the localization of the epileptogenic zone (Kalitzin et al., 2012).
2.6 Conclusions

We present here a new algorithm for detection of HFOs, which was trained on one patient and tested on five other patients. The process of selecting events of interest in the time domain in a first stage focused on high sensitivity. Good specificity in HFO detection was achieved in a second stage by recognizing time-frequency characteristics of individual HFOs. Ranking channels by HFO rate and selecting only those above half-maximum rate resulted in good specificity for detection of the SOZ. The sensitivity for detection of the SOZ by this algorithm was markedly higher than with RMS and LineLength detectors in four patients and equal in two patients. The computational run-time on a PC allows – in principle - an online implementation. Together with the reasonable accuracy, this holds promise for the diagnostic value of the detector for intraoperative recordings.
Chapter 3. Classification of high frequency oscillations in synthetic data

This chapter describes the application of principal component analysis (PCA) and neural networks for separation of HFOs from the sharp spikes and artifacts in EEG data. Algorithms for classification were trained and tested on simulated data, which consisted of HFOs (sine waves of different frequency), sharp spikes (with triangle or Gaussian shape) and combinations of these two events.

This work was presented at the Lab meeting at Institute of Neuroinformatics on November 12th, 2014.

3.1 Introduction

Several recent studies using macro-electrodes have recorded HFOs either in isolation or in association with interictal spikes in different types of human epilepsies. The algorithm presented in Chapter 1 for detection of HFOs based on filtering EEG signals in high frequency band using standard band-pass filters.

However, the use of standard filtering methods raises some methodological issues (Benar et al., 2010). Some brain signals are not limited to frequency bands, and the energy of these signals spreads over the whole frequency spectrum. This is especially a case for sharp transients, such as epileptic spikes or impulse-like artifacts. These events are defined as broadband events. The energy of the ideal short duration transient signal is distributed uniformly over all frequencies. After band-pass filtering, transient events have a signal very similar to the impulse response of the filter, which is commonly a short-duration oscillation. As an effect, filtered sharp transient events can result in “false” ripples that can be easily confounded with true ripples.

The algorithm presented in Chapter 2 aimed to avoid this issue. In order to improve the detector, we applied classification algorithms based on PCA and neuronal networks in order to separate true HFOs from wrongly marked sharp transients, such as epileptic spikes and artifacts. Neural networks trained on synthetic data allow automatic detection and separation of HFOs without human intervention.
3.2 Data synthesis

In order to train and test the algorithms, we simulated the data with events such as HFOs and sharp spikes.

For simulation of HFOs we used the sine waves with frequencies in the range of 80-450 Hz with 4-6 oscillations to fulfill the requirements for HFOs (Jacobs et al., 2012).

For simulation of epileptic spike, we used sharp (10-40 ms) spike with triangle or Gaussian shape with different amplitude and different duration (“sharpness”) (Figure 3.1).

For simulation of pure HFOs we used sine waves with frequencies in the range of 100-450 Hz, having at least four full oscillations.

The detector presented in Chapter 2 was based on the assumption that the HFO appears as a separate blob on the time-frequency plot (Figure 2.1). The pure spike or the artifact produces a single elongated shape with no visible band-limited blob (Benar et al., 2010) (Figures 2.2, 2.3, 3.1).
The ultimate goal was to detect the HFO event, which is superimposed on the sharp spike. In this case, the blob corresponding to the pure spike has high amplitude, and its extent into the high frequency bands could mask a pure HFO event (Figure 2.2).

Figure 3.2 Simulated sharp triangle spikes with an HFO. Examples of the Gaussian spike occurring together with an HFO (left column) and separately (right column). The HFO “blob” can be masked by the wide frequency extent of the sharp spike.
3.3 Classification of events

After simulation of events, we trained the algorithms based on several features. As all events are first detected by Stage 1 of the algorithm described in Chapter 1, for each event we extracted three features: duration, maximum amplitude of raw and filtered signal. Additionally, we fitted the Hilbert envelope, which was calculated on the filtered signal, with the Gaussian fit (2 features). This resulted in 5 features from the time domain (Figure 3.3 A, B).

Further, we transposed the raw signal into the time-frequency domain (Figure 3.3 C). We fitted the average power spectrum (over duration of the detected event) by a sum of 3 Gaussian terms (MATLAB, function gauss3) (Figure 3.4 D). We chose especially 3 terms as we expect to have up to three independent components in the signal (background activity, spike and HFO). This resulted in 9 features from the time-frequency domain.

Figure 3.4 Feature extraction. (A) Example of an HFO superimposed on a spike. (B) Filtered signal (blue) together with the Hilbert envelope (red) and Gaussian fitting of the envelope (green). (C) The Stockwell transform of the raw signal. (D) Average power spectrum (blue) with a fit of sums of three Gaussian terms (red).
After extraction of features, we first implemented the PCA in order to show that HFOs (either pure or superimposed on a spike) can be separated into two independent classes using the features chosen. Figure 3.5 shows the results of the PCA.

![Figure 3.5 Results of PCA.](image)

After implementing PCA, we trained the algorithm on the neural network. As a result, the algorithm showed good classification accuracy on a large dataset of simulated events.

### 3.4 Conclusions

We showed direct evidence for the existence of distinct classes of sharp epileptic spikes and HFOs, which can be superimposed on the spike or occur independently, in a synthetized data. Neural networks trained on synthetized data showed high accuracy and allow automatic classification of pure spikes and HFOs without human intervention. The algorithm was not validated on visually marked events in real data, because we found out that both kinds of events (spikes and HFOs) similarly reflect epileptogenicity and both must be considered to delineate the epileptogenic zone (Chapter 4).
Chapter 4. The morphology of high frequency oscillations does not improve delineating the epileptogenic zone

This chapter describes further development of the automated detector. The detector was trained, calibrated and tested on a dataset of visually marked HFOs. Additionally, it was shown that the regularity and irregularity in amplitude of HFOs similarly reflects the epileptogenicity, and it is not necessary to separate real HFOs from “false oscillations” produced by the filter effect of sharp spikes (Benar et al., 2010). The detector was also evaluated with respect to the surgical outcome on a set of patients different from the one it had been developed on.

This work was published in Clinical Neurophysiology (Burnos et al., 2016). I present here the final version of the manuscript prior to publication.

4.1 Abstract

Objective: We hypothesized that high frequency oscillations (HFOs) with irregular amplitude and frequency more specifically reflect epileptogenicity than HFOs with stable amplitude and frequency.

Methods: We developed a fully automatic algorithm to detect HFOs and classify them based on their morphology, with types defined according to regularity in amplitude and frequency: type 1 with regular amplitude and frequency; type 2 with irregular amplitude, which could result from filtering of sharp spikes; type 3 with irregular frequency; and type 4 with irregular amplitude and frequency. We investigated the association of different HFO types with the seizure onset zone (SOZ), resected area and surgical outcome.

Results: HFO rates of all types were significantly higher inside the SOZ than outside. HFO types 1 and 2 were strongly correlated to each other and showed the highest rates among all HFOs. Their occurrence was highly associated with the SOZ, resected area and surgical outcome. The automatic detection emulated visual markings with 93% true positives and 57% false detections.

Conclusions: HFO types 1 and 2 similarly reflect epileptogenicity.

Significance: For clinical application, it may not be necessary to separate real HFOs from “false oscillations” produced by the filter effect of sharp spikes. Also for automatically detected HFOs, surgical outcome is better when locations with higher HFO rates are included in the resection.
Chapter 4. The morphology of HFOs does not improve delineating the epileptogenic zone

4.2 Introduction

In many patients with therapy-refractory focal epilepsy, surgical resection of the epileptogenic zone represents the therapeutic option of choice. Currently, the identification of the seizure onset zone (SOZ) is used for delineating the epileptogenic zone (Rosenow and Lüders, 2001). Over the last years, high frequency oscillations (HFOs) have been proposed as a novel indicator for the epileptogenic zone (Urrestarazu et al., 2007; Jacobs et al., 2012; Zijlmans et al., 2012b). HFOs are defined as spontaneous EEG patterns in the frequency range between 80-500 Hz, consisting of at least four oscillations that clearly stand out of the background activity (Jacobs et al., 2012). Interictal HFOs proved to be more specific in localizing the SOZ than spikes (Jacobs et al., 2008) and have shown a good correlation with the postsurgical outcome in epilepsy patients (Jacobs et al., 2010a; Wu et al., 2010; Akiyama et al., 2011; van ’t Klooster et al., 2015).

HFOs are differentiated into “ripples” (80-250 Hz) and “fast ripples” (FRs, 250-500 Hz) (Bragin et al., 1999b). FRs are considered more specific for epileptogenicity because of their close relation to the SOZ (Engel et al., 2009). Ripples were shown to be a less specific marker of the epileptogenic zone than FRs regarding the surgical outcome (Akiyama et al., 2011; van ’t Klooster et al., 2015). This is best explained by the fact that there are not only epileptic and hence pathological ripples, but also spontaneous physiological ripples generated by the healthy brain. It was shown that the hippocampus generates ripples associated with memory consolidation during sleep and rest (Girardeau and Zugaro, 2011). Spontaneous ripples were additionally found in the human visual cortex and the paracentral areas (Nagasawa et al., 2012; Wang et al., 2013). There are several reports of HFO induction in the human visual cortex (Matsumoto et al., 2013; Kucewicz et al., 2014), the auditory cortex (Edwards et al., 2005), the motor cortex (Darvas et al., 2010) and the language areas (Sinai et al., 2005). Event-related FRs can be recorded in humans during median nerve stimulation (Maegaki et al., 2000) or during cognitive processing (Kucewicz et al., 2014). Consequently, most clinical studies on ripples probably analyzed a mixture of physiological and pathological HFOs. Moreover, usually only the rates of HFOs are considered important for localizing epileptogenic areas.

There are several reports on the separation of pathological and physiological HFOs. Matsumoto et al. (2013) recorded event-related physiological HFOs in specific neocortical areas, induced by sensory stimulation or by motor tasks and compared them with spontaneous presumably pathological HFOs recorded from the SOZ. The authors parameterized each HFO according to the spectral amplitude, frequency and duration and then classified both types of HFOs using these parameters with a support vector machine. Pathological HFOs in the SOZ were highly distinguishable from physiologically induced HFOs in the defined feature space. Although the data provided a statistical difference between the two groups of HFO, they did not assist in the classification of an individual HFO because of the large overlap between the groups.
Another approach based on the association of HFOs with slow waves during sleep is presented in Frauscher et al. (2015). Frauscher and co-authors showed an increased facilitation of epileptic HFOs during high amplitude slow waves. Interestingly, they found that HFOs inside the SOZ coupled differently to the slow wave than HFOs in presumably normal channels. This difference in coupling was confirmed in a recent study in 45 patients (von Ellenrieder et al., 2016).

One possible approach to separate pathological and physiological HFOs would be to consider the different types of HFOs. Wang et al. (2013) classified ripples according to their presence with interictal epileptiform discharges (IED). The authors hypothesized that because IEDs are not normal physiologic events, HFOs occurring simultaneously with IEDs are assumed more specific for epileptogenicity. The authors showed that ripples superimposed on IEDs precisely marked the SOZ. In contrast, ripples independent of IEDs did not correlate with the SOZ.

Another approach based on the background activity was presented in (Kerber et al., 2013). The authors showed that resection of areas with ripples occurring in a flat background activity correlates with a good postsurgical outcome, whereas resection of areas generating ripples in a continuously oscillating background did not show an association with the surgical outcome.

Melani et al. (2013) investigated continuous high frequency activity in the ripple band. They observed this high frequency activity in channels outside the SOZ or a lesion, most exclusively in the hippocampus and occipital cortex. The authors concluded that the high frequency activity they had described is of physiological nature and independent of epileptogenicity.

In this study we aimed 1) to define different types of HFOs based on their morphological appearance, and 2) to investigate whether the respective types have a different association with the SOZ, resected area and surgical outcome. We hypothesized that HFOs with irregular amplitude and frequency might more specifically reflect epileptogenicity than HFOs with stable amplitude and frequency. This reflects our clinical experience where we see regular HFOs also in physiological areas and irregular HFOs co-occur with spikes or with FRs, which are associated with pathological areas. To perform this analysis in a standardized way, we developed a fully automatic algorithm to detect and classify HFOs.

### 4.3 Patients and methods

#### 4.3.1 Patient datasets

We used three different datasets. Table 4.1 describes each dataset in detail.

Dataset 1 was used to define different types of HFOs based on their morphological appearance. This dataset only consisted of channels inside the SOZ of 20 patients with medically intractable uni- or bilateral mesiotemporal lobe epilepsy, who underwent depth electrode implantation (electrodes either manufactured on site (9 contacts, 0.5 - 1 mm in
Chapter 4. The morphology of HFOs does not improve delineating the epileptogenic zone

The morphology of HFOs does not improve delineating the epileptogenic zone

length and separated by 5 mm) or commercially available (5 - 18 contacts, 2 mm in length, separated by 1.5 mm, DIXI Medical, France) at the Montreal Neurological Institute and Hospital. The intracranial EEG (iEEG) was recorded with the Harmonie EEG system (Stellate, Montreal, Canada), with a low-pass filter of 500 Hz and a sampling rate of 2000 Hz. For each patient, a five-minute NREM sleep segment in one channel located in the SOZ was analyzed (Frauscher et al., 2016).

Dataset 2 was used for the validation of the automatic HFO detector. This dataset was used before for the comparison of different HFO detectors (Zelmann et al., 2012). Nineteen patients with intractable epilepsy were implanted and recorded in the same way as Dataset 1. The Dataset 2 consisted of 19 one-minute sections, each with 10-39 channels, for a total of 373 channels. This dataset includes channels from inside and outside of the SOZ.

<table>
<thead>
<tr>
<th>Dataset</th>
<th>N patient</th>
<th>N channels</th>
<th>Location</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20</td>
<td>20</td>
<td>SOZ in mTLE</td>
<td>(Frauscher et al., 2016)</td>
</tr>
<tr>
<td>2</td>
<td>19</td>
<td>373</td>
<td>TLE, ETE</td>
<td>(Zelmann et al., 2012)</td>
</tr>
<tr>
<td>3</td>
<td>30</td>
<td>1355</td>
<td>29 TLE, 9 ETLE</td>
<td>(Haegelen et al., 2013)</td>
</tr>
</tbody>
</table>

Table 4.1 Information on the three datasets investigated in this study. SOZ seizure onset zone; ETE extratemporal lobe epilepsy; mTLE mesial temporal lobe epilepsy; TLE temporal lobe epilepsy.

Dataset 3 was used for investigating whether the different HFO types have a specific association with the SOZ, resected area and surgical outcome. This dataset was used before for evaluating the impact of removing HFO-generating tissue on surgical outcome (Haegelen et al., 2013). Thirty patients with intractable epilepsy were implanted and recorded in the same way as Datasets 1 and 2. Information about the SOZ, resected area and surgical outcome (with a postoperative follow-up of at least 9 months) was known. The dataset 3 consisted of 1355 channels, from which 248 were in the SOZ (1107 outside) and 347 in the resected area (1008 outside). We analyzed intervals of iEEG of five-minute length. According to the International League Against Epilepsy (ILAE) classification (Wieser et al., 2001), 15 patients had a good outcome (ILAE 1-3), and 15 had a poor outcome (ILAE 4-6).

Regarding the patient groups, there is a partial overlap between Datasets 1-3. We used recordings from total of 50 patients, and 15 of them were used more than once. Surgical decision was based on clinical information in combination with results of neuroimaging, identified SOZ in iEEG investigation and presence of eloquent cortex. Rates of interictal HFOs were not considered in the decision making process.

4.3.2 Visual definition of types of HFOs

The visual marking of HFOs was performed in the Stellate viewer by splitting the screen vertically, resulting in raw iEEG on the left side and 80 Hz high-pass filtered iEEG on the right side of the screen with time resolution of 0.6 sec across the monitor. For the marking,
the filtered signal on the right side was considered, the unfiltered signal on the left served only for the differentiation from artifacts. Different from the original analysis (Jacobs et al., 2009), we visualized only one channel.

The detected HFOs were then visually reviewed by three experts (SB, BF, JG) on Dataset 1. Visual analysis based on regularity in amplitude and frequency of the filtered signal >80 Hz revealed four different types of HFO (Figure 4.1).

Type 1 HFOs (Figure 4.1, panel (1 A-C)) are regular HFOs, with regular amplitude and frequency (Figure 4.1, panel (1 B)).

Type 2 HFOs (Figure 4.1, panel (2, 3 A-C)) are HFOs with irregular amplitude and one outstanding peak and with regular frequency (Figure 4.1, panel (2, 3 B)). After visual review of raw data, we assumed that this peak could be a result of filtering of the sharp components of the IED (Benar et al., 2010) (Figure 4.1, panel 2 A-C), but it could also reflect true ripple activity. Type 2 HFOs do not necessary co-occur with an IED (Figure 4.1, panel 3 A-C).

Type 3 HFOs (Figure 4.1, panel (4 A-C)) are HFOs with regular amplitude but irregular frequency (Figure 4.1, panel (4 B)). After visual review of filtered (>80 Hz) data, we observed ripples with varying frequency (Figure 4.1, panel 4 B). Many HFOs of this type have components in a wide frequency range, i.e. ripple and FR (Figure 4.1, panel 4 C) co-occurrence. This latter type is also in line with the literature where it was shown that the majority of FRs (68-91%) is superimposed with ripples (Urrestarazu et al., 2007; Wang et al., 2013).

Type 4 HFOs (Figure 4.1, panel (5 A-C)) are HFOs with irregular amplitude and frequency (Figure 4.1, panel (5 B)). This type is a combination of type 2 HFO and a FR. Type 4 HFOs can be a wide-frequency (80-500Hz) filtering effect of a sharp component of an IED.

Because of the previous clinical experience, we hypothesized that type 1 HFOs with regular amplitude and frequency was more physiological, as we observed them also in physiological areas (Nagasawa et al., 2012). Additionally, type 2 HFOs with irregular amplitude often co-occurred with spikes and, because of the spike pathological nature, we expected type 2 HFOs to be more pathological (Wang et al., 2013). Type 3 and type 4 HFOs included a FR, which was shown to be a very specific indicator of epileptogenicity (van ’t Klooster et al., 2015). Therefore, types 3 and 4 HFOs were thought to be associated with pathological activity.
Chapter 4. The morphology of HFOs does not improve delineating the epileptogenic zone

Figure 4.1 Representative examples of the four HFO type. (A) 0.3 sec epoch of a raw intracranial EEG bipolar channel. (B) High-pass (>80 Hz) filtered intracranial EEG of panel A. (C) High-pass (>250 Hz) filtered intracranial EEG of panel A. (1 A-C) Example of a type 1 HFO with regular amplitude and frequency. (2 A-C) Example of a type 2 HFO at the time of a spike. The irregular amplitude of the HFO could be due to a filter effect of the sharp spike. (3 A-C) Example of a type 2 HFO occurring independently of a spike. We observe an irregular amplitude HFO with one outstanding peak. Note that this peak is similar to that observed in the context of a spike. (4 A-C) Example of a type 3 HFO with irregular frequency, with activity in both frequency ranges (4B, 4C). (5 A-C) Example of a type 4 HFO, with irregular amplitude and irregular frequency.
4.3.3 Automatic detector

In the automatic detection stage, we detected events in a similar way as the visual reviewer. We adapted the automatic detector from (Burnos et al., 2014) and used Dataset 2 with 373 channels for training and testing the detector. Similar to (Zelmann et al., 2012), we randomly chose 20% (76) of channels for training, resulting in 297 channels for evaluating the detector performance. The automatic detector consists of two steps – the baseline detector and the detector of HFOs.

4.3.3.1 Band-pass filters

The automatic detector separately identified ripples and FRs. For the detection of ripples, the iEEG was band-pass filtered (80-250 Hz) using a FIR equiripple filter (fStop1 = 70 Hz, fPass1 = 80Hz, fPass2 = 240 Hz, fStop2 = 250 Hz, stopband attenuation = -60 dB). For the detection of FRs, the iEEG was band-pass filtered (250-500 Hz) using a FIR equiripple filter (fStop1 = 240 Hz, fPass1 = 250Hz, fPass2 = 490 Hz, fStop2 = 500 Hz, stopband attenuation = -60 dB).

4.3.3.2 Baseline detection

We defined the baseline as segments of iEEG with no oscillatory activity of any kind. The baseline detector is similar to (Zelmann et al., 2010), which is based on wavelet entropy (Rosso et al., 2001). We used entropy based on the Stockwell-transform (Stockwell et al., 1996), which measures the degree of randomness (vs. oscillatory activity) in the signal. The maximum theoretical Stockwell entropy (SE_{max}) is obtained for white noise, when contributions at all frequency ranges are equal. We considered a segment as a baseline (i.e. no oscillation present) when the Stockwell entropy was larger than 90% of the SE_{max}.

4.3.3.3 HFO detection

In the step of HFO detection, we detected HFOs based on the amplitude of the filtered signal. We calculated the envelope using the Hilbert transform (Crepon et al., 2010; Burnos et al., 2014). An event was marked when the envelope exceeded a threshold (Staba et al., 2002; Gardner et al., 2007). The threshold was defined as a percentile of the cumulative distribution of the amplitude of the Hilbert envelope taken for baseline segments (ThrHilbEnv, same for ripple and FR detection). This and the following procedure is different from (Burnos et al., 2014). The duration of the event was defined as the interval between upward and downward crossing of 0.5*threshold. If its duration exceeded 20 ms for ripples and 10 ms for FRs, this event was qualified as an HFO. We merged HFOs with an inter-event-interval of less than 10 ms into one single HFO. HFOs not having a minimum of 6 consecutive peaks (band-passed signal rectified >0 V) greater than a threshold were rejected. The threshold was chosen at a percentile of the cumulative distribution of the band-passed signal for baseline segments (ThrFiltRipple and ThrFiltFR, different for ripple and FR detection).
4.3.3.4 Parameter optimization

The HFO detection step was optimized to maximize sensitivity with respect to visual markings. All detected HFOs outside of any visual marking were assumed as wrong detections. With respect to that, we followed (Zelmann et al., 2012) and calculated the True Positive Rate (TPR) as the number of HFOs detected visually and automatically divided by the total number of visually detected HFOs. We calculated the False Detection Rate (FDR) as the number of automatically detected HFOs that are outside any visually marked HFO event divided by the total number of automatically detected HFOs. We optimized three thresholds ThrHilbEnv, ThrFiltRipple and ThrFiltFR.

Receiver operating characteristic (ROC) curves measure the performance of the detector when varying these three thresholds and were used for the evaluation of the detector. The parameters, which gives the TPR=1 and FDR=0 (top left corner), represent the perfect decision maker.

4.3.4 Automatic HFO classifier

In the automatic classification stage, we separated detected HFOs into four types, similar to those defined for visual review.

We checked the HFO for irregularity in amplitude. We compared the global maximum of the filtered HFO event (>80 Hz) to the nearest local maxima. We defined the ratio between global and local maxima as the threshold to differentiate type 1 HFOs with regular amplitude and type 2 HFOs with irregular amplitude. After training, the optimum threshold was set to 2.

In order to assess irregularity in frequency, we checked if an automatically detected FR occurred in the time interval of the HFO. We defined type 3 HFOs as HFOs occurring simultaneously with a FR.

An HFO with both irregular amplitude and frequency was classified as type 4.

For the training of the classifier, we used 5 patients from Dataset 1. We used another 15 patients from Dataset 1 for validation of the classifier. The first 50 HFOs in each patient were visually classified by an expert (BF), who was blind to the automatic classification results. In three patients we identified only 29, 32 and 41 HFOs in the 5-minute recordings. The agreement between the viewer and the classifier was calculated based on the four types of HFOs.

4.3.5 Analysis of Dataset 3

We finally applied the optimized automatic detector and classifier on Dataset 3. We calculated the rates of HFOs together with rates of HFOs of each type for all channels. We compared rates of HFOs of each type in channels inside and outside the SOZ and the resected area. Additionally, we tested whether the surgical resection of channels carrying HFOs of each type was correlated with a good postsurgical outcome and, conversely, whether a non-resection of the HFO channels resulted in poor postsurgical outcome. If not stated otherwise, the rates are presented in median [range] HFOs/min.
4.3.6 Statistical analysis

We used the Wilcoxon rank sum test to compare rates of HFOs of each type in channels inside versus outside the SOZ and in channels inside versus outside the resected area. We also calculated the ratio between rates of HFOs of each type in resected (Res) and non-resected (nonRes) channels, using the following formula (Haegelen et al., 2013):

\[
\frac{\bar{R}_{ev}(\text{Res}) - \bar{R}_{ev}(\text{nonRes})}{\bar{R}_{ev}(\text{Res}) + \bar{R}_{ev}(\text{nonRes})},
\]

where \(\bar{R}\) is the mean rate of an event (ev, HFO type 1-4). A ratio of +1 indicates that the HFO generating areas have been completely resected. A ratio of -1 indicates that no HFO generating area has been resected.

We used the Wilcoxon rank sum test to compare the ratios of events between patients with a good and poor outcome. We expect that ratios would be close to +1 in patients with a good outcome and close to -1 in patients with a poor outcome. The Spearman’s rho was used to explore correlations between rates of HFOs of different types in channels inside the SOZ. Statistical significance was established for \(p<0.05\). All statistics were corrected for multiple comparisons by the Bonferroni-Holm method.

4.4 Results

4.4.1 Accuracy of the detector

The accuracy of the detector in emulating visual marking was determined in Dataset 2. We used this dataset because it was already used to compare different HFO detectors (Zelmann et al., 2012). With optimal parameter settings we obtained TPR = 77±30% and FDR = 28±27%, which were closest to the left top corner of the ROC-plot. However, we preferred to choose parameters such that TPR = 93±15% [95% confidence interval 91-95%] and FDR = 58±27% [55-60%], so that the TPR was comparable to the MNI detector (Zelmann et al., 2012) and more events were available for subsequent analysis.

The visual and the automatic classification into HFO types agreed well, with an inter-rater reliability of mean 79%, median [range] 82% [54-96%] in Dataset 1 (N=15 patients).

4.4.2 HFO types and the SOZ

Dataset 3 has been used previously to evaluate the impact of removing the HFO-generating tissue on surgical outcome (Haegelen et al., 2013). We aimed to replicate this analysis by the automatic detection and by differentiating between HFO types. In Dataset 3 we found 115884 HFOs, from which 85525 (74%) were type 1 HFOs, 2074 (17%) type 2 HFOs, 2969 (3%) type 3 HFOs and 7316 (6%) type 4 HFOs. When analyzing all HFOs together, the rates were significantly higher inside the SOZ than outside the SOZ: 25.6 [0-204.4] vs. 2.8 [0-191.6] HFOs/min, \(p<0.001\).
In the separate analysis of HFO types (Figure 4.2), the rates of HFO of each type were significantly higher inside the SOZ than outside the SOZ. For type 1 HFOs, rates were 17.7 [0-187.4] vs. 2 [0-173.4] HFOs/min; type 2 – 3.9 [0-63] vs. 0.2 [0-55] HFOs/min; type 3 – 0.4 [0-18.4] vs. 0 [0-9] HFOs/min; and type 4 – 0.4 [0-27.2] vs. 0 [0-53.8] HFOs/min; all p<0.001. The rates of type 3 and type 4 HFOs were very low and we excluded these two HFO types from further analysis.

Additionally, we calculated the correlation between rates of different HFO types across channels inside the SOZ. Figure 4.3 shows the correlation between rates of different types of HFOs across channels in the SOZ. We found a high correlation between all HFO types (correlation type 1 and type 2 – Spearman’s rho=0.85; type 1-3 rho=0.69; type 1-4 rho=0.55; type 2-3 rho=0.74; type 2-4 rho=0.69; type 3-4 rho=0.84, all p<0.001).
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4.4.3 HFO types and the surgical resection

Figure 4.3 shows results of the comparison of HFOs rates of each type against the resected area in Dataset 3. When analyzing all HFOs together, the rates were significantly higher inside the resected area than outside: 7 [0–158.4] vs. 3.6 [0–204.4] HFOs/min, p<0.001.

Also in the separate analysis of HFO types, the rates of HFO of each type were significantly higher inside the resected area than outside. For type 1 HFOs, rates were 5 [0–127.6] vs. 2.6 [0–187.4] HFOs/min, p<0.001. For type 2 HFOs, rates were 0.8 [0–51.4] vs. 0.4 [0–63] HFOs/min, p<0.001.

Figure 4.3 Correlation between rates of different HFO types across channels inside the SOZ. The black dashed line is the linear fit. We found a high correlation between all HFO types. Correlation between type 1 and type 2 HFO – Spearman’s rho=0.85; type 1-3 rho=0.69; type 1-4 rho=0.55; type 2-3 rho=0.74; type 2-4 rho=0.69; type 3-4 rho=0.84; all p<0.001.

Figure 4.4 shows results of the comparison of HFOs rates of each type against the resected area in Dataset 3. When analyzing all HFOs together, the rates were significantly higher inside the resected area than outside: 7 [0–158.4] vs. 3.6 [0–204.4] HFOs/min, p<0.001.

Also in the separate analysis of HFO types, the rates of HFO of each type were significantly higher inside the resected area than outside. For type 1 HFOs, rates were 5 [0–127.6] vs. 2.6 [0–187.4] HFOs/min, p<0.001. For type 2 HFOs, rates were 0.8 [0–51.4] vs. 0.4 [0–63] HFOs/min, p<0.001.

Figure 4.4 Comparison of rates of the different HFO types against surgical resection. Boxplots illustrating rates of all HFOs and types 1-2 HFO in channels inside the resected area (Res, N=347) and outside (nonRes, N=1008). The rates of all HFOs together and the rates of the HFOs of each type were significantly higher inside the resected area than outside. The red numbers present the number of outliers exceeding the maximum rate of the y-axis. *p≤0.05, **p≤0.001.
4.4.4 HFOs and the surgical outcome

Figure 4.5 shows results of the comparison of the ratio of HFO rates of each type against the surgical outcome in Dataset 3. We found that the ratio between HFO rates in resected and non-resected channels was significantly higher in patients with a good outcome (ILAE classes 1-3) compared to patients with a poor outcome (ILAE classes 4-6) (median [range]: 0.3 [-0.8 – 1] vs. 0.0 [-1 – 0.3], p=0.016, after the Bonferroni-Holm correction).

When subdividing the analysis by HFO types, results were marginally significant with the Bonferroni-Holms correction (p=0.056) and were significant if we did not do the Bonferroni-Holm correction, which is how most other studies have been done. The ratio between HFO rates in resected and non-resected channels was significantly higher in patients with a good outcome than in patients with a poor outcome for type 1 HFOs (median [range]: 0.1 [-0.8 – 1] vs. -0.1 [-1 – 0.3], p=0.028), and for type 2 HFOs: 0.4 [-1 – 1] vs. 0.0 [-1 – 0.4] (p=0.031). There was thus no difference with respect to outcome between type 1 and type 2 HFOs.

4.5 Discussion

Our classification of HFOs according to their morphology showed that all four HFO types reflect epileptogenicity equally well since all types of HFO are highly associated with the SOZ. We could also show that the most frequently occurring HFO types (1 and 2) are associated with the resected area and the surgical outcome.
Chapter 4. The morphology of HFOs does not improve delineating the epileptogenic zone

In our fully automatic application on Dataset 3, we found that rates of HFOs were higher inside the SOZ, and resection of areas with higher HFO rates predicted good surgical outcome. These two results agree with results obtained with the visual marking reported in the same dataset (Haegelen et al., 2013).

4.5.1 Properties of the four HFO types

Type 1 HFOs were by far the most frequent (74% of all HFOs in Dataset 3). Because their amplitude and frequency is very regular, we had initially hypothesized that type 1 HFOs are less specific for epileptogenicity. This hypothesis was not confirmed, since all four HFO types predicted outcome equally well. We now consider that type 1 HFOs can be found in both pathological as well as physiological conditions, albeit the rate is much higher in the epileptogenic zone compared to the normal zone.

Type 2 HFOs represented 17% of all HFOs. The visual and automatic detection of this HFO type is challenging, because its irregular amplitude could be either an effect of filtering sharp epileptiform spikes (“false ripple”, (Benar et al., 2010)) or a ripple superimposed on a sharp spike (Amiri et al., 2015). We showed that type 1 and type 2 HFO rates are highly correlated (Figure 4.3) and reflect epileptogenic activity equally well. We speculate that higher rates of the type 2 HFOs in the SOZ and resected area could result from high spike rates or from spike sharpness. It was shown in Hufnagel et al. (2000) that the shortest spike duration and the maximal spike frequency were highly associated with a zone ≤2 cm from the SOZ.

HFOs of type 3 and 4 are composed of both a ripple and a fast component resembling an FR (Figure 4.1). FRs in the post resection iEEG were good predictors of recurrent seizures (van 't Klooster et al., 2015). The broad frequency and amplitude range of type 4 HFO could result from artifacts. Since HFOs of type 3 and 4 only represent 9% of all HFOs, the predictive power of HFOs would remain favorable even if we exclude them from the analysis.

4.5.2 Association of HFOs with the SOZ, the resected area and the surgical outcome

All HFO types were strongly associated with the SOZ, even though the rates of type 3 and type 4 HFO were very low. High correlations between HFO types in SOZ channels support the fact that all HFO types carry similar information about epileptogenicity. Because of the low rates of HFO type 3 and type 4 we used only type 1 and type 2 HFO for the analysis of HFO rates in the resected area.

All HFOs together, and also type 1 and type 2 HFO separately, were strongly associated with the resected area. In extension of the analysis of (Haegelen et al., 2013), we found that rates of HFOs of each type were significantly higher in the resected area. This is an expected result as the resected area and the SOZ are closely overlapping.

Good surgical outcome was associated with the resection of channels with high rates of HFOs, using all HFOs of all types. This was significant also after applying the Bonferroni-
Holm correction, which places a stricter requirement on statistical significance than most other publications on this topic.

In a separate analysis of type 1 and type 2 HFOs, association of good surgical outcome with the resection of channels with high rates of HFOs type 1 and type 2 were marginally significant ($p=0.056$) with the Bonferroni-Holm correction. The separate analysis was significant without the Bonferroni-Holm correction, as it is done in most other publications on this topic. Given that the smaller number of events maybe the cause of this marginal significance, we conclude that there is a good chance that both types are good indicators for the epileptogenic zone.

### 4.5.3 Automatic detector

The automatic detector we presented here has several important features, which distinguish it from existing detectors. We used two different frequency ranges in order to detect separately ripples and FRs. The aim of our detector was to detect only visually marked events and to have the least possible number of false detections. In comparison to the MNI detector (Zelmann et al., 2012), which has the best performance among several existing detectors, our detector has a slightly lower sensitivity (93% vs. 98%) and lower FDR (58% vs. 76%) in dataset 2.

How does the FDR affect our analysis in dataset 3, where there was no visual marking? Some of the “false” HFOs detected may represent pure epileptic spikes. It is true that the detector detects events in dataset 3 that may not have been marked by human interpreters, but these events are nevertheless classified according to the algorithm into the 4 categories and each has therefore the characteristics of one of the 4 HFO types. Detected HFOs will fall in type 2 if they have a good chance of resulting from spike filtering. Additionally, it has been shown that spikes inside the SOZ are sharper and shorter than outside (Hufnagel et al., 2000), which increases this chance. It may therefore be that the epileptogenic zone is strongly associated with true HFOs as well as with sharp spikes, which appear as “false” HFOs after filtering.

### 4.5.4 Other approaches to discriminate physiological and pathological HFOs

The approach we presented here is novel and different from the existing ones (Kerber et al., 2013; Wang et al., 2013) as it is based exclusively on the morphology of HFOs, and not based on relation to spikes or background activity. For more accurate comparison and delineation of pathological and physiological HFOs, one should compare rates of different HFO types of cortical tissue without epilepsy.
4.6 Conclusions

All four HFO types are highly associated with the SOZ. The strong correlation between type 1 and type 2 HFOs together with their association with the SOZ, resected area and surgical outcome show that both HFO types similarly reflect epileptogenic activity. The exclusion of HFO type 3 and 4 has probably no influence on the results, because of their low rates and similar association with the SOZ. For clinical application, it may not be necessary to separate real HFOs from “false oscillations” produced by the filter effect of sharp spikes since type 2 HFOs, which includes most such oscillations, have the same association with the epileptogenic zone as the more regular type 1 HFOs. The surgical outcome is better when locations with higher HFO rates are included in the resection. This standardized analysis relied on a newly developed and fully automated HFO detection method.
Chapter 4. The morphology of HFOs does not improve delineating the epileptogenic zone
Chapter 5. Automated detection of high frequency oscillations predicts seizure freedom in individual patients

This chapter covers clinical evaluation of the automated detector. The detector was trained on a dataset of visually marked HFOs on one dataset of patients (Burnos et al., 2016) and then was evaluated with respect to the surgery outcome on a different dataset of patients. Areas of the brain with high HFO rates were shown to be associated with the epileptogenic zone. A clinical application of the automatically detected HFOs for prediction of seizure freedom in epilepsy patients was shown.

This work was submitted to Nature Communications (Burnos et al., submitted). I present here a more extended version of the manuscript prior to submission.

5.1 Abstract

Objective: While HFOs are gaining acceptance as biomarkers of the epileptogenic zone (EZ), the value of their fully automated detection for surgical planning is still debated.

Methods: Presurgical invasive recordings were collected in 16 patients, 7 with mesial temporal lobe epilepsy (TLE) and 9 with extratemporal epilepsy (ETE). Recordings were analyzed with an automated detector, which was validated on visually marked datasets. Analyses were conducted separately for ripple (80-250 Hz) and fast ripple (FR, 250-500 Hz) frequency ranges. Resection of areas with HFO rates above the threshold were related to the seizure outcome.

Results: FRs co-occurring with ripples (FRandR) were associated with the EZ and were more specific than ripples and FRs separately in the prediction of seizure outcome in individual patients. Resection of FRandR areas correctly predicted seizure freedom in all 11 patients. In one of five patients with recurrent seizures, FRandR-containing cortex was not resected. In the group analysis of TLE and ETE patients, all types of HFOs had higher rates inside the resected area than outside.

Conclusions: The resection of areas characterized by co-occurrence of FRs and ripples predicts seizure freedom in individual patients with temporal and extratemporal lobe epilepsy. The fully automated procedure standardizes the definition of a clinically relevant HFO and may aid in surgical planning.
5.2 Introduction

In patients with drug-resistant focal epilepsy, surgical resection of the epileptogenic zone (EZ) is the therapeutic option of choice. Currently, the identification of any epileptogenic lesion and of the seizure onset zone (SOZ) is used to delineate the EZ (Rosenow and Lüders, 2001). Over the last years, high frequency oscillations (HFOs) recorded in intracranial EEG (iEEG) have been proposed as a novel indicator for the EZ (Urrestarazu et al., 2007; Jacobs et al., 2012; Zijlmans et al., 2012b). HFOs are defined as spontaneous EEG patterns in the frequency range between 80-500 Hz that consist of at least four oscillations that clearly stand out of the background activity (Jacobs et al., 2012). HFOs are differentiated into “ripples” (80-250 Hz) and “fast ripples” (FRs, 250-500 Hz) (Bragin et al., 1999b). Interictal HFOs proved to be more specific in localizing the SOZ than spikes (Jacobs et al., 2008) and have shown a good correlation with the post-surgery outcome in epilepsy patients (Jacobs et al., 2010a; Wu et al., 2010; Akiyama et al., 2011; van ’t Klooster et al., 2015). While both ripples and FRs are associated with the EZ, their co-occurrence was not investigated yet.

To standardize and facilitate HFO analysis several algorithms for automated or semi-automated detection of HFOs have been proposed (Staba et al., 2004; Gardner et al., 2007; Crepon et al., 2010; Dümpelmann et al., 2012; Zelmann et al., 2012; Birot et al., 2013; Burnos et al., 2014). While earlier detectors rely rather on thresholds in the time domain, a number of recent detectors also incorporate the frequency domain, which is computationally more demanding (Birot et al., 2013; Burnos et al., 2014; Burnos et al., 2016; Fedele et al., 2016).

Currently, there is no evidence on how HFOs, detected in a fully automated way, can affect surgery planning. Studying the iEEG for ripples, FRs and their co-occurrence is needed to establish the value of HFOs for surgical planning of the resection. In this study we hypothesize that resection of HFOs, detected in a fully automated and standardized way, can predict seizure freedom in individual patients. We applied the automated detector (Burnos et al., 2016) and evaluated the clinical relevance of HFOs by comparing areas with sufficiently high HFO rates with the resected area (RA) and seizure outcome.

5.3 Materials and methods

5.3.1 Patient selection

We included all 16 patients with drug-resistant focal epilepsy, who were implanted with intracranial electrodes from March 2012 to March 2015 and had a surgical resection together with a postoperative follow-up > 1 year (Table 5.1). Of these 16 patients, 7 had mesial temporal lobe epilepsy (TLE) and 9 had extratemporal epilepsy (ETE). According to
the International League Against Epilepsy (ILAE) classification (Wieser et al., 2001), 11 patients were completely seizure free (ILAE 1), and 5 had recurrent seizures (ILAE 2-6).

5.3.1 Ethics statement
Collection of personal patient data and retrospective scientific workup was approved by the institutional ethics review board (Kantonale Ethikkommission KEK-ZH-Nr. 2012-0212) and collection of patients’ written informed consent was waived.

5.3.2 Electrode types and implantation sites
Intracranial depth macro electrodes and subdural strips and grids were implanted at locations planned according to the results of the non-invasive presurgical work-up (Figure 5.1A,B).

For TLE patients, depth electrodes (1.3 mm diameter, 8 contacts of 1.6 mm length, spacing between contacts centers 5 mm, ADTech, www.adtechmedical.com) were implanted stereotactically into the amygdala, the hippocampal head and the entorhinal and perirhinal cortex bilaterally.

For ETE patients, a combination of depth and subdural strip and grid electrodes (contact diameter 4 mm with a 2.3 mm exposure, spacing between contact centers 10 mm) was placed after craniotomy. Here depth electrodes were implanted into the supposed center of bottom-of-sulcus dysplasias as defined by morphometric postprocessing of MR images (Wellmer et al., 2010). Post-implantation MR images were used to locate each contact anatomically along the electrode trajectory.

5.3.3 Surgical planning
The decision for surgical resection was based the standardized protocol we follow at our center. This comprises clinical information, neuroimaging (including morphometric postprocessing of MRI data), psychiatric and neuropsychological examinations (including fMRI and Wada-tests where indicated) as well as non-invasive and invasive video-/EEG-monitoring and if necessary electrostimulation mapping of eloquent cortex. The HFO analysis did not enter the decision making process.

5.3.4 Data acquisition
The iEEG was recorded for presurgical evaluation starting from the day after electrode implantation. The recording was performed in the intensive monitoring unit under continuous video surveillance. Intracranial data was acquired at 4000 Hz with an ATLAS recording system (0.5-1000 Hz pass-band, Neuralynx, www.neuralynx.com) and downsampling to 2000 Hz for HFO analysis. In addition, scalp EEG and the submental electromyogram (EMG) were recorded. The iEEG was recorded against a common reference and then transformed to a bipolar montage for further analysis.
### Table 5.1 Patient characteristics.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age, y</th>
<th>Gender</th>
<th>Histology/Pathology</th>
<th>Epilepsy</th>
<th>Electrode placement</th>
<th>Type of electrodes</th>
<th>Surgery</th>
<th>Ripple area resected?</th>
<th>FR area resected?</th>
<th>FRandR area resected?</th>
<th>Outcome ILAE</th>
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<td>1</td>
<td>25</td>
<td>M</td>
<td>HS; gliosis</td>
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<td>2 strips 6x1; 1 depth</td>
<td>Les</td>
<td>Y</td>
<td>Y</td>
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<td>36</td>
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</tbody>
</table>

**Table 5.1 Patient characteristics.** Abbreviations: C = central; ETE = extratemporal lobe epilepsy; F = frontal; FCD = focal cortical dysplasia; FR = fast ripple; FRandR = FR occurring together with ripple; HFO = high frequency oscillation; HS = hippocampus sclerosis; ILAE = International League Against Epilepsy; MTL = mesial temporal lobe; L = left; Lat = lateral; Les = lesionectomy; P = parietal; Pr = precentral; R = right; SAHE = selective amygdala-hippocampectomy; TLE = mesial temporal lobe epilepsy.

### 5.3.5 Data selection

We selected for each patient five minutes of interictal slow-wave sleep, which minimizes muscle activity and enhances HFO rates (Staba et al., 2004; Bagshaw et al., 2009). Sleep scoring was performed based on scalp EEG, electrooculogram, EMG and video recordings. We chose time intervals that were isolated from epileptic seizures by at least three hours to eliminate the influence of seizures on our analysis.
5.3.6 Automated detection of HFOs

We analyzed HFOs in iEEG using two automated detectors, which had been trained, tested and validated on datasets from Montreal Neurological Hospital and Institute (Burnos et al., 2016) and from University Medical Center Utrecht (Fedele et al., 2016). Both detectors were adapted from (Burnos et al., 2014), which was developed on data from six patients from the Swiss Epilepsy Centre in Zurich.

The HFO analysis (Figure 5.1D) was conducted separately for ripples (band-pass 80-240Hz, stopband 70Hz and 250Hz) and FRs (band-pass 250-490Hz, stopband 240Hz and 500Hz). In both cases we used FIR equiripple filter with stopband attenuation 60 dB.

Both detectors incorporate information from both time and frequency domain and operate in two stages. In the first stage – baseline detection – we detected baseline segments without any oscillatory activity by the Stockwell entropy distribution and defined the amplitude threshold above the baseline level (Stockwell et al., 1996; Rosso et al., 2001; Zelmann et al., 2012). In the second stage – HFO detection – we labeled those events as HFOs where the envelope of the filtered signal exceeded the amplitude threshold for at least 20 ms for ripples and 10 ms for FRs.

The Morphology detector was trained and tested to detect events like the visual reviewer (Burnos et al., 2016). The test and validation datasets included data recorded from depth electrodes only. To analyze data from subdural electrodes in the present study, we adapted the ripple threshold (ThrFiltRip=0.99), while all other parameters remained the same. The code is freely available at the HFO detectors repository on github (https://github.com/HFO-detect/HFO-detect-matlab).

The Stockwell detector was designed to detect clinically relevant HFOs, particularly in the FRs frequency range (Fedele et al., 2016). After detection, events of interest were projected into the time-frequency domain by the Stockwell transform. If the event had a distinct peak in the instantaneous amplitude spectrum, it was validated as a putative HFO. Finally, for each HFO we checked the spatial distribution of the correlation across channels. If the correlation coefficient across channels exceeded 0.8 on a distance larger than 2 cm for ripples and 1 cm for FRs, the putative HFO was rejected as an artifact.

The major difference between detectors, apart from the HFO definition is stage 2, is that they were trained, tested and validated on datasets, which were recorded from different epilepsy centers and marked by different expert viewers.

5.3.7 Definition of the HFO area by thresholding

We computed the rates of automatically detected HFOs in the iEEG. In each patient, we analyzed the spatial distribution of HFO rates across channels. We defined the HFO area as the ensemble of only those channels whose rates exceeded the threshold (95 percentile of the HFO rate distribution, Figure 5.1E). We identified an HFO area for three types of HFOs: ripples, FRs and FRs co-occurring together with ripples (FRandR). For each HFO type, we evaluated the clinical relevance of the HFO area for the delineation of the EZ.
Figure 5.1 Automated HFO analysis of patient 4. (A) Presurgical MRI shows right hippocampal sclerosis (HS). (B) MRI after the implantation of 8 depth electrodes sampling the mesial temporal structures. (C) MRI after right selective amygdala-hippocampectomy, resulting in long-term seizure freedom. (D) Example of a ripple co-occurring with a FR (FRandR, green line). (E, F, G) The HFO types differ in their distribution over channels. Given the neuroradiological diagnosis of this patient, we considered only the contacts located in the mesial temporal structures for further analysis, i.e. the three most internal contacts of each electrode. Note that several channels have FRandR rate = 0. Channels with rates above the 95 percentile (black horizontal line) were taken to define the HFO area. Channels inside the resected area (RA) are shown in red, channels outside the RA (nRA) in blue. The ripple area was not resected (E). The resection of the FRandR area (G, channel AR1-AR2) led to seizure freedom. Implantation sites: AL amygdala left; AR amygdala right; EL entorhinal cortex left; ER entorhinal cortex right; HL anterior hippocampus left; HR anterior hippocampus right; PL posterior hippocampus left; PR posterior hippocampus left.
5.3.8 Prediction of seizure outcome

We quantified the predictive value of the HFO area with respect to seizure outcome (Table 5.2). Automated HFO detection and analysis were blind to clinical information. We defined as true positive (TP) a patient who was seizure free and where the HFO area was fully located within the RA, i.e. the whole HFO area was resected. We defined as false positive (FP) a patient who was seizure free but where the HFO area was not fully located inside the RA, i.e. at least one channel of the HFO area was not resected. We defined as false negative (FN) a patient with recurrent seizures and the HFO area fully located within the RA, and as true negative (TN) a patient with recurrent seizures and the HFO area not fully located inside the RA. The positive predictive value was calculated as $\text{PPV} = \frac{\text{TP}}{\text{TP} + \text{FP}} \times 100\%$, the negative predictive value as $\text{NPV} = \frac{\text{TN}}{\text{TN} + \text{FN}} \times 100\%$. 95% confidence intervals (CI) were estimated based on the binomial distribution. We used the values of the PPV and the NPV to quantify how the resection of fully automatically detected HFO areas predicts epilepsy surgery outcome.

5.3.9 Comparison between HFO rates inside and outside the RA

In order to show the association of FRandR with the EZ, we compared the FRandR rates inside and outside the RA in individual patients with seizure freedom, since the EZ in these patients was correctly identified and fully resected. In a group analysis of TLE and ETE seizure free patients, we compared the rates of all HFO types inside and outside the RA.

5.3.10 Statistical analysis

We used the paired Wilcoxon signed rank test to compare median FRandR rates inside and outside the RA in individual patients. We used the Mann-Whitney U test to compare HFO rates of all types inside and outside the RA in the group analysis. Statistical significance was established for $p<0.05$. All statistics were corrected for multiple comparisons by the Bonferroni-Holm method.

5.4 Results

We first present the automated HFO analysis in individual patients. We identified the HFO area and evaluated the association with the RA and the seizure outcome. We then compared median FRandR rates inside and outside the RA in individual patients. Additionally, we compared HFO rates inside and outside the RA in a group analysis of patients with TLE and ETE.
5.4.1 Prediction of seizure outcome

Table 5.2 shows the predictive values of the automated detector (the Morphology detector), defined for three types of HFOs in all 16 patients. Resection of ripple areas (section 5.3.8) correctly predicted seizure freedom in 6/11 patients (PPV = 55%, CI [23-83%]); resection of FR areas correctly predicted seizure freedom in 8/11 patients (PPV = 73%, CI [39-94%]); resection of FRandR areas correctly predicted seizure freedom in 11/11 patients (PPV = 100%, CI [72-100%]). Ripple, FRs and FRandR analysis gave NPV = 20%, CI [0-72%] (1/5 patients). Resection of the FRandR area thus had the best predictive power for seizure outcome.

The Stockwell detector showed similar results for prediction of the seizure outcome.

<table>
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<tr>
<th>Seizure free N=11</th>
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<th>FRandR</th>
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<td>11</td>
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<tr>
<td>Patient seizure free</td>
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<td>0</td>
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<tr>
<td>Patient seizure free</td>
<td>HFO area not fully located in RA</td>
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<tr>
<td>Positive predictive value PPV [%]</td>
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<td>73</td>
<td>100</td>
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<tr>
<td>Confidence Interval CI [%]</td>
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<tr>
<th>Not seizure free N=5</th>
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<tbody>
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<td>4</td>
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<tr>
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<td>Negative predictive value NPV [%]</td>
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<tr>
<td>Confidence Interval CI [%]</td>
<td>0-72</td>
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</tbody>
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Table 5.2 Predictive value of automatically detected HFO area using the Morphology detector. Abbreviations: CI = confidence interval; FR = fast ripple; FRandR = FR co-occurring with ripple; HFO = high frequency oscillation; RA = resected area.

5.4.2 Agreement between the HFO area and RA

Over all 16 patients, the ripple area was included in the RA in 10 patients (agreement 63%), FR area in 12 patients (75%) and FRandR area in 15 patients (94%). The FRandR area thus agreed best with the surgeon’s actual resection.
5.4.3 FRandR rates and the RA in individual seizure free patients

Since FRandR had the best predictive power across patients, we compared the FRandR rates inside and outside the RA in individual patients with seizure freedom, since the EZ in these patients was correctly identified and fully resected. In the analysis of individual patients (Figure 5.2), we found that the median rate of FRandR was significantly higher inside the RA than outside (2.3 range [0-16] vs. 0.3 range [0-1] HFOs/min, p=0.014). High rates of FRandR were thus associated with the EZ in individual patients.

![Figure 5.2 Median FRandR rates inside and outside the RA in individual patients.](image)

**Figure 5.2** Median FRandR rates inside and outside the RA in individual patients. Median rates of FRandR were significantly higher inside the RA than outside in 10 patients with seizure freedom (paired Wilcoxon signed rank test p<0.001). Abbreviations: ETE = extratemporal epilepsy; nRA = not resected area; RA = resected area; TLE = mesial temporal lobe epilepsy.

5.4.4 HFO rates and the RA in a group analysis of TLE and ETE patients

In a group analysis of TLE and ETE patients, we compared the rates of all HFO types inside and outside the RA (Figure 5.3).

In the group analysis of TLE patients (Figure 5.3A), rates of FRs and FRandR were significantly higher inside the RA than outside: FRs 3.8 [1-70] vs. 2.6 [0-13] HFOs/min, p<0.001; FRandR 0.2 [0-38] vs. 0 [0-7] HFOs/min, p=0.013.

In the group analysis of ETE patients (Figure 5.3B), rates of HFOs of each type were significantly higher inside the RA than outside: ripple 37.4 [8-247] vs. 19 [0-264] HFOs/min, p<0.001; FRs 14.6 [3-49] vs. 3.2 [0-29] HFOs/min, p<0.001; FRandR 2 [0-16] vs. 0.2 [0-10] HFOs/min, p<0.001.
For both TLE and ETE patients, high rates of HFOs were thus associated with the RA.

5.5 Discussion

We introduced FRandR as a predictor of seizure freedom in individual patients with either TLE or ETE. Moreover, we quantified the clinical relevance of our fully automated and standardized analysis by correlating the HFO area to the RA and to seizure outcome.

FRs are considered more specific for epileptogenicity than ripples because of their close relation to the SOZ (Engel et al., 2009) and to the seizure outcome (Akiyama et al., 2011; van ’t Klooster et al., 2015). Surprisingly, co-occurrence of FRs and ripples was not evaluated before. We proved that FRandR are more specific in the prediction of seizure freedom than ripples and FRs separately in individual patients. The association of the FRandR and EZ was visible even in individual patients.

As a main strength of our study, the specificity of FRandR provided a high PPV with narrow confidence intervals. Such high predictive power not only generalizes the value of FRandR across different types of patients, but also holds true at the level of the individual patient. Different from other studies that consider only the SOZ, we based our analysis on post-surgical seizure freedom, which is more relevant for clinical decisions.

FRandR correctly predicted seizure freedom in 11/11 patients (PPV 100%). In all seizure free patients with ETE (pts 8-13) the RA was limited to 1-2 cm3 even though the SOZ extended also to eloquent cortex. The SOZ was not fully resected. In contrast, the HFO area defined by FRandR was always fully resected. Thus, the FRandR were clearly more specific markers of the EZ than the SOZ.
While the NPV is indeed low, it is mainly determined by the span of the implanted electrodes. In our HFO analysis, in 4 of the 5 patients with recurrent seizures the HFO area was included to the RA. In the remaining patient (pat 15) the HFO area was not fully resected, and our HFO analysis may possibly be superior to the standard decision (Figure 5.4). Patients 5 and 6 had missed the intake of one antiepileptic drug dosage and consequently suffered a recurrent seizure (ILAE 3). In the other two patients with recurrent seizures (pat 7, 16) the HFO area was fully included in the RA. Given the same iEEG information available, our HFO analysis was at least as good as the standard decision making process.

The automated analysis standardizes the definition of an HFO, which allows an unbiased evaluation of the clinical relevance of HFOs. HFO analysis performed by expert observers suffers from time consuming visual marking and lacks reproducibility (Höller et al., 2015). The best validation for HFO analysis is its comparison with post-surgical outcome. To date, only a few studies correlated automated HFO rating with patients’ outcome (Burnos et al., 2016; Fedele et al., 2016). Our algorithm used here was trained and tested on datasets from different epilepsy centers and marked by different expert viewers (Burnos et al., 2016). As a major advance over previous studies, we applied here a fully automated procedure. With minimal clinical information and minimal human monitoring of data quality, our automated algorithm analyzed iEEG signal and delineated the HFO area by HFO detection and thresholding. The high PPV of our algorithm makes it suitable for localizing the EZ in future data sets.
Chapter 5. Automated detection of HFOs predicts seizure freedom in individual patients

To check the consistency of the automated detection, we additionally applied the Stockwell detector, which was designed to detect clinically relevant HFOs, particularly in the FRs frequency range (Fedele et al., 2016). The Stockwell detector showed similar results, which is promising as it points to the robustness of the results of the automated detection.

To compare our data with the literature, we also fed our individual patients into a group analysis (Figure 5.3). Our results agree with previous studies (Haegelen et al., 2013; Kerber et al., 2013), whereby we have improved the analysis by a fully automated HFO detection.

We believe that the information provided by HFOs could contribute to surgical planning especially in patients with FCD. The exact extent of these pathologies, sometimes challenging to detect in MRI (Krsek et al., 2008), is difficult to predict even with postprocessing of the images (Huppertz et al., 2005). Therefore, the evidence for using complementary electrophysiological markers as HFO analysis is rising (Wu et al., 2010; van 't Klooster et al., 2015). Future research should concentrate on collecting further confirmations of the clinical reliability of HFOs, in particular FR and R. We showed that the resection of areas generating HFOs, specifically FR and R, detected in a fully automated and standardized way, predicts good seizure outcome in individual patients with either TLE or ETE. We showed an association of FR and R with the EZ in individual patients.

5.6 Conclusions

The resection of areas characterized by co-occurrence of FRs and ripples predicts good seizure outcome in individual patients with temporal and extratemporal lobe epilepsy. The HFO analysis could have improved the outcome in one patient with recurrent seizures. Our fully automated procedure standardizes the definition of a clinically relevant HFO, which is a prerequisite before HFOs can guide surgical treatment in multicenter studies.
Chapter 6. Outlook

In this thesis, the automated detector of HFOs was developed and validated on intracranial EEG recordings. Currently, the detector is used in the following ongoing projects.

6.1 Intracranial EEG recordings during surgery

From a neurosurgical perspective, it is important that HFOs can aid in the decision-making during epilepsy surgery. The automated detector was applied on the intraoperative EEG data recorded at the University Medical Center Utrecht (UMCU, (Fedele et al., 2016)), and showed high predictive power for post-surgical outcome. In order to achieve higher rates of HFOs, the detector was applied on the low-noise intracranial EEG recordings during surgery the University Hospital Zurich (Fedele et al., submitted).

In the long run, the low computational time of the automated HFO detector allows an online analysis by collecting all necessary information during surgery, and therefore presurgical diagnostics would no more be necessary. In this way, HFO analysis can potentially reduce recording time and also risk for patients.

6.2 Epileptic ripples in MEG recordings

The algorithm presented here is not limited only to EEG signals, but can be applied for detection of HFOs also in virtual sensors of MEG at University Medical Center Utrecht (Figure 6.1, (van Klink et al., submitted)). In MEG signals, the detection of HFOs is impeded by noise, their low occurrence rates and the workload of visual analysis. The automated HFO detector together with algorithms for noise reduction and beamforming can identify and localize ripples in MEG with minimal human effort. This would allow defining the epileptogenic zone with high spatial resolution.

Figure 6.1 Example of an automatically detected HFO in MEG signals.
6.3 Monitoring the efficacy of antiepileptic therapy in scalp EEG

Currently, the efficacy of each antiepileptic drug regarding seizure control is commonly established based on self-reported seizure frequency, which is, however, unreliable. Thus, surrogate biomarkers offering high reliability and practicability are urgently needed to evaluate treatment effect.

The HFOs, and in particular FRs as a reliable biomarker of epileptogenicity, were recorded in the scalp EEG. The FRs possibly can be automatically detected with sufficient accuracy to monitor the efficacy of the antiepileptic therapy.

As a first step, ongoing application of the detector comprises detection of HFOs in non-invasive scalp EEG using optimized low-noise recording technology (Fedele et al., 2012). In the next step, the combination of automated detector and low-noise recording system should be applied in a large number of patients in order to assess the rates of FRs that can be expected. Figure 6.2 shows an example of the application of the automated HFO detector on the low-noise scalp EEG recordings.

![Figure 6.2 Example of an automatically detected HFO in low-noise scalp EEG recording. (A) Raw data (B) Filtered (250-500 Hz) signals. The detected HFO is marked in red.](image)

In the long run, the project envisions a combination of the low-noise EEG recordings with automated HFO detection that can be applied for real-time therapy monitoring in epilepsy patients (Figure 6.3). Overall, spontaneous scalp FRs are most likely to be recorded in children, since their FRs have higher amplitudes and rates. The results are thus expected to have a high impact first on children and subsequently also adult patients.

![Figure 6.3 A vision of non-invasive real-time therapy monitoring of epilepsy patients.](image)
Chapter 7. General conclusions

We have developed a new fully automated robust algorithm for detection of HFOs and have evaluated the clinical value of this detector for planning epilepsy surgery.

As a new approach, the HFO detector makes use of the instantaneous power spectrum as calculated by the Stockwell transform (Chapter 2). We showed that HFO events, detected by the automated algorithm, were associated with the seizure onset zone and therefore clinically relevant.

The definition of a baseline is a crucial first step for any HFO detection. As a major advance over existing detectors, we used the instantaneous power spectrum of the Stockwell transform to estimate the instantaneous entropy of the signal (Section 4.3.3.2). Segments with high entropy, i.e. without oscillatory activity, turned out to provide the most reliable baseline. This definition of the baseline improved drastically the detector’s performance, especially in signals with continuous high frequency activity.

The improved detector proved valuable, first, in a collaborative project with the Montreal Neurological Institute at McGill University, where we obtained a high reliability when reproducing visual markings in a large set of preoperative recordings (Chapter 4).

Next, in a collaboration with University Medical Center Utrecht, we showed the association of automatically detected HFOs with seizure freedom in intraoperative recordings of individual patients (Fedele et al., 2016).

Finally, we applied the detector on the Zurich dataset of preoperative recordings. While other research groups (Jacobs et al., 2010a; Haegelen et al., 2013) compare visually detected HFOs with the post-surgical outcome on the group level, we proved the value of automated HFOs for prediction of seizure freedom in individual patients (Chapter 5).

Ongoing application of the algorithm detector comprises detection of HFOs in EEG recorded non-invasively from the scalp in Montreal, Freiburg and Zurich. The algorithm is not limited to EEG signals, but detects HFO also in virtual sensors of MEG from University Medical Center Utrecht (van Klink et al., submitted).

The application of the automated detector standardizes the definition of HFOs, which allows rigorous testing of their clinical relevance, also between epilepsy centers. We showed the potential of automated HFO detection to improve surgery planning. We believe that the detector might become a complimentary clinical diagnostic tool for the precise localization of the epileptogenic zone in epilepsy patients.
Bibliography


