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Simultaneously recorded intracranial and scalp high frequency oscillations help identify patients with poor postsurgical seizure outcome

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HIGHLIGHTS

- Scalp high frequency oscillations (HFO) localize the seizure onset zone in refractory epilepsy.
- Widespread scalp HFO are indicative of large epileptic network.
- Scalp HFO analysis might help predict postsurgical seizure outcome.

ABSTRACT

Objective: High frequency oscillations (HFO) between 80–500 Hz are markers of epileptic areas in intracranial and maybe also scalp EEG. We investigate simultaneous recordings of scalp and intracranial EEG and hypothesize that scalp HFOs provide important additional clinical information in the presurgical setting.
Methods: Spikes and HFOs were visually identified in all intracranial scalp EEG channels. Analysis of correlation of event location between intracranial and scalp EEG as well as relationship between events and the SOZ and zone of surgical removal was performed.
Results: 24 patients could be included, 23 showed spikes and 19 HFOs on scalp recordings. In 15/19 patients highest scalp HFO rate was located over the implantation side, with 13 patients having the highest scalp and intracranial HFO rate over the same region. 17 patients underwent surgery, 7 became seizure free. Patients with poor post-operative outcome showed significantly more regions with HFO than those with seizure free outcome.
Conclusions: Scalp HFOs are mostly located over the SOZ. Widespread scalp HFOs are indicative of a larger epileptic network and associated with poor postsurgical outcome.
Significance: Analysis of scalp HFO add clinically important information about the extent of epileptic areas during presurgical simultaneous scalp and intracranial EEG recordings.

1. Introduction

Around one third of patients with focal epilepsy continue to have seizures even after therapy with several different antiepileptic drugs (Kwan and Brodie, 2000). In these patients epilepsy surgery aiming to remove the epileptic focus is a very effective treatment to stop seizures permanently (Rosenow and Lüders, 2001). In some patients non-invasive diagnostic such as MRI and long-term EEG do not lead to conclusive results regarding the epileptic focus. In these patients intracranial chronic EEG recording may be used to delineate the seizure onset zone (SOZ) and define which brain areas have to be removed to have a good postsurgical seizure outcome (Diehl and Lüders, 2000).

Intracranial EEG recordings have a very high spatial resolution in the brain areas which are covered by electrodes, but for practical reasons they can only sample small portions of the brain. Therefore invasive EEG may miss epileptic activity deriving from brain areas not covered by electrodes. The recording of simultaneous scalp EEG during the intracranial EEG may help to identify ictal epileptic

Abbreviations: EEG, electro-enzephalography; FCD, focal cortical dysplasia; HFO, high frequency oscillation; MRT, magnet resonance tomography; SOZ, seizure onset zone.

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activity far from the electrode sites. A seizure free postsurgical outcome might be less likely in patients with widespread intracranial and scalp EEG activity at the beginning of seizure.

High frequency oscillations (HFO) are new EEG markers of epileptic tissue (Jacobs et al., 2012). They are distinct short oscillatory events in two frequency ranges, called ripples if they occur in the frequency band of 80–250 Hz and fast ripples in the frequency band of 250–500 Hz. HFOs most often occur in the SOZ zone (Jacobs et al., 2008, 2009; Worrell et al., 2008; Crépon et al., 2010) and the surgical removal of areas which generate HFOs is associated with a better seizure outcome (Ochi et al., 2007; Jacobs et al., 2010; Wu et al., 2010; Akiyama et al., 2011; van't Klooster et al., 2015). While first described in invasive microelectrode recordings in Kainic acid-treated rats (Bragin et al., 1999b) and epileptic humans (Bragin et al., 1999a) as well as macroelectrode recordings in epileptic humans (Jirsch et al., 2006; Jacobs et al., 2008), HFOs have recently also been analyzed in scalp EEG. These scalp HFO were less common than intracranial HFO, mostly observed in the ripple frequency range and more localized to the SOZ than epileptic spikes (Andrade-Valenca et al., 2011; Melani et al., 2013). In a first simultaneous intracranial and scalp EEG study it could be proven that HFOs on the scalp have intracranial matching HFO correlates (Zelmann et al., 2013). Simulation studies confirmed the hypothesis that background activity level in scalp EEG recordings (one of the most important contributors to the noise) decreases with frequency. As a consequence, some small generators of high frequency activity can produce scalp signals that are as easy to detect as typical IEDs (von Ellenrieder et al., 2014). This applies especially to HFO in the ripple band as for the frequency band of fast ripple, the increasing electronic noise generated by measuring amplifiers becomes more relevant (Fedele et al., 2017a). Although visual detection of HFO in scalp EEG is a time consuming task (Andrade-Valenca et al., 2011; Zelmann et al., 2013) and expert raters are needed to allow for good inter-rater agreement (Gardner et al., 2007), a complementary use of scalp HFOs could be useful to identify patients in whom the epileptogenic zone exceeds brain areas covered with intracranial electrodes. In the present study we systematically analyzed the simultaneous scalp EEG of patients undergoing chronic intracranial EEG recordings. It is hypothesized that patients with a wide spread occurrence of scalp HFO are less likely to profit from epilepsy surgery than those with very focal HFO generation.

2. Methods

2.1. Patient recruitment and clinical data

During a one year period 37 patients underwent intracranial EEG investigations at the Freiburg epilepsy center. Inclusion criteria for the current study were the following:

- Application of scalp electrodes during the intracranial investigation.
- Possibility to select an EEG segment which was recorded with 2000 Hz sampling rate.
- Possibility to select a period of slow wave sleep with a distance of at least 2 hrs from and to the next seizure.

This study was approved by the Freiburg Ethics Commission and all patients signed informed consent.

All clinical data from individual patients was taken from the electronic patient charts. Areas of seizure onset were defined by the clinical neurophysiologist as part of the clinical routine and independently of the research study. A surgical decision was made in the interdisciplinary clinical meeting of the Epilepsy center as a result of the intracranial EEG evaluation. Patients underwent postsurgical follow up in the outpatient clinic at 3, 6 and 12 months after surgery. Postsurgical outcome was determined using the Engel classification (Engel et al., 1993). The postsurgical MRT at 3 months after surgery was aligned with the presurgical MRI to determine which regions under which electrode contacts could be considered removed.

28 patients had simultaneous scalp electrode recordings; four had to be excluded for failure to identify an EEG segment which met the inclusion criteria. Four patients had subdural grid and/or strip electrodes, 15 patients depth electrodes and five a combination of subdural and depth electrodes. Clinical details of the patients is provided in Table 1.

2.2. EEG recording and segment selection

Intracranial EEG was recorded either using stereotactically implanted depth electrodes or subdurally placed grid electrodes (AD-TECH Medical Instrument Corporation, Racine, WI, USA). Intracranial EEG was recorded using the software Profusion EEG (Compumedics Limited, Abbotsford Victoria, Australia) using a high pass filter of 1.6 Hz as well as a low pass filter of 800 Hz and a sampling rate of 2000 Hz. A reference and a ground electrode were placed according to the positions AF1 and AF2 of the international 10–10 system, respectively. Additional scalp EEG contacts were placed according to the international 10–20 system, resulting in 21 electrodes (not including ground and reference) per patient. Scalp EEG was recorded using a high pass filter of 0.5 Hz and a low pass filter of 800 Hz, and a sampling rate of 2000 Hz. Reference and ground electrode were the same as for iEEG. Sleep staging was performed using the Software Profusion PSG 3 (Compumedics Limited, Abbotsford Victoria, Australia). During recording of the scalp EEG, impedances were checked regularly und kept below 5 kΩ.

A two hour segment was selected during slow wave sleep. The latter was identified as period with 2 Hz delta waves with an amplitude of a minimum of 75 μV. Periods were selected in which the next seizure was at least two hours away. If possible, the first night of the recording was selected to avoid influences of reduced antiepileptic drugs. iEEG and scalp HFO have been marked during the same 10 minute segment of the preselected 2 h of slow wave sleep. To allow for analysis of a longer EEG segment, the first of the two preselected hours of slow wave sleep was marked for epileptic spikes in scalp EEG. During this segment each spike was analyzed for associated scalp ripple.

2.3. Identification of HFO

Intracranial HFOs were marked using Harmonie Monitoring System (Stellate, Montréal, Canada) in a 10 min EEG segment using a bipolar montage as has been described previously (Jacobs et al., 2008). In short ripples were identified using a 80 Hz FIR high pass filter and fast ripples were defined as oscillations which are visible with a 250 Hz FIR high pass filter and at the same time not visible in the 80 Hz filtered EEG. Rates of ripples and fast ripples were calculated for each channel.

Scalp HFOs were marked on all channels after scalp electrodes were placed according to the international 10–20 system using a bipolar montage. Channels with continuous recording artifacts were excluded. HFOs were marked using a 80 Hz FIR high pass filter and a split screen. On the other side of the screen the unfiltered EEG was visualized, all segments which had clear muscle, eye blink or movement artifacts were identified and excluded from further analysis. For every possible HFO seen in the filtered EEG, this section in the unfiltered EEG was visualized with extended time line and increased gain to make sure that the electrode trace was free of small artifacts (Jacobs et al., 2016). In the case of uncertainty

Table 1
Clinical information.

#	m/f	age	Seizure type	MRI	Type of Implantation	AED	Type of surgery	Outcome Engel
1	f	30	CPS, GTCS	DNET FL	DE	LTG, PGB	Lesionectomy FL	2
2	m	53	CPS, GTCS	Arachnoid cyst L O	Subdural	LEV, PT, CLB	Cortial topectomy FR	1
3	m	28	SPS, CPS GTCS	temporo-polarer encephalocele L	DE	LTG, ZNS	Lesionectomy plus T pole	2
4	m	28	SPS, CPS	Non-lesional	DE, subdural	LTG, OXC, CLB	No surgery	–
5	f	28	CPS, GTCS	Ganglioglioma L T	DE, subdural	LAC	lesionectomy	1
6	f	48	CPS	Non-lesional	DE	ZNS	sAHE R	2
7	m	50	CPS	Non-lesional	Subdural	LEV, OXC	No surgery	–
8	m	14	SPS, CPS, GTCS	FCD gyrus frontalis inferior, orbitalis posterior and lateralis L	Subdural	LEV, LTG	Lobectomy FL	3
9	f	55	SPS, CPS, GTCS	Non-lesional	DE	LEV, LAC, PGB	Topectomy FL	2
10	f	47	SPS	Non-Lesional	Subdural	ZON, LTG	Topectomy PR	2
11	f	63	CPS, GTCS	Bilateral menigo-encephalocele T pole	DE	LTG	Lesionectomy Tpole L	1
12	m	32	CPS, GTCS	Cavernoma Gyrus cinguli R, FCD mesio-temporal left	DE	LAC, LTG, CLB	Lesionectomy L	1
13	f	32	CPS	MTS bilateral	DE	PRG, LC, RTG	No surgery	–
14	m	39	CPS, GTCS	MTS right	DE, subdural	LEV, CBZ	sAHE R	4
15	f	43	CPS, GTCS	Posttraumatic lesion FP L	DE	LTG	No surgery	–
16	f	30	SPS, CPS, GTCS	Atrophy F R	DE	LAC, PGB, LTG	Topectomy FR	4
17	m	55	SPS, CPS, GTCS	Non-lesional	DE, subdural	LEV, ESC	Topectomy PL	2
18	f	19	CPS	FCD bilateral F	DE	LEV, OXC	No surgery	–
19	f	33	CPS, GTCS	Non-lesional	DE	OXC, TPM	Lobectomy TR	1
20	f	20	SPS, CPS	MTS and FCD L T	DE, subdural	OXC, LEV	Lobectomy T L	1
21	f	47	CPS, GTCS	Multiple postraumatic lesions F L	DE	VGB, LEV, PGB, RTG	Topectomy FR	4
22	m	23	CPS	Non-Lesional	DE	LVA, OXC, PHB	No surgery	–
23	m	21	CPS, GTCS	Non-lesional	DE	OXC, ZON	Topectomy FR	1
24	m	47	CPS	FCD gyrus supramarginal is R	DE	OXC, LVA, PRG	Lesionectomy FR	3

Abbreviations: CBZ = Carbamazepine, CLB = Clobazam, CPS = complex partial seizure, DE = depth electrode, ESC = Eslicarbazepinacetat, F = frontal, f = female, FCD = focal cortical dysplasia, GCTS = generalized tonic clonic seizure, L = left, LAC = lacosamide, LEV = levetiracetam, LTG = lamotrigine, m = male, MTS = mesio-temporal sclerosis, OXC = oxcarbazepine, P = parietal, PGB = pregabalin, PHB = phenobarbital, PT = phenytoin, R = right, RTG = Retigabin, SPS = simple partial seizure, T = temporal, TPM = Topiramat, VGB = vigabatin, VPA = valproat acid, ZNS = zonisamide.

we decided to be highly specific and disregard the possible event. Only events agreed upon by two experienced raters after individual visual analysis were accepted as HFO. Fig. 1 gives an example of a scalp ripple as well as a typical artifact. Additionally all epileptic spikes were marked in the unfiltered EEG.

To allow for analysis of a longer EEG segment, the first of the two preselected hours of slow wave sleep was marked for epileptic spikes. During this segment each spike was analyzed for associated scalp ripple.

Rates for intracranial and scalp HFOs as well as co-occurrence with epileptic spikes was calculated for each channel using Matlab software (The Mathworks Inc., Natick, Massachussetss, USA).

The seizure onset zone (SOZ) was determined independently from this study by the treating neurologists in the Epilepsy Centre and consisted of those contacts of the iEEG and the scalp EEG respectively, which showed initial seizure activity. For statistics regarding the side of implantation, all channels over the respective brain lobe of the implantation were considered.

2.4. Statistical analysis

For HFOs a Wilcoxon Ranksum test was performed to compare HFO rates inside and outside the seizure onset zone. Significance level was set at $p < 0.05$.

Additionally intracranial and scalp HFO occurrences were compared. For this purpose, areas of scalp HFOs were classified as either occurring ipsilateral, contralateral or bilateral to the intracranial implantation side, as well as the defined intracranial SOZ. Furthermore, EEG contacts (scalp and intracranial) were assigned to different brain lobes, contacts belonging to the same brain lobe were considered "corresponding". For comparison, the areas with the highest HFO rates were defined as the channel with the highest HFO rate in an individual patient and all additional channels in this patient which had a rate of at least 90% of the one with the highest rate.

In patients who underwent surgery, additionally the extent of scalp HFOs was correlated with the postsurgical outcome to test the hypothesis that a large extend of HFOs on scalp EEG might indicate a more widespread epileptic network and a poor prognosis for surgery. For this purpose, every scalp contact of the 10–20-montage was assigned as belonging to a certain brain lobe (e.g. Fp1, F3 → left frontal lobe; T4, T6 → right temporal lobe O1 → left occipital lobe etc.). In a second step, all EEG Channels were assessed as showing HFO or not and in accordance to their belonging to a certain brain region as "surgically removed" or not.

3. Results

In total, 24 patients were implanted with three to sixteen electrodes resulting in a total number of 2408 analyzed intracranial channels. 576 scalp channels were recorded, of which 42 had to be excluded due to poor recording quality.

3.1. HFO occurrence in intracranial and scalp EEG

All patients showed intracranial ripples and fast ripples. Ripple rates were significantly higher in the SOZ (26.0 ± 35.4 R/min) than outside the SOZ (15.8 ± 31.4 R/min, $p < 0.001$). Fast ripples were also significantly higher inside (1.9 ± 4.1 FR/min) than outside the SOZ (1.7 ± 3.4 FR/min, $p < 0.001$, see Fig. 2).

19 patients showed ripples in the scalp EEG (10 minute segment), with ripple amplitudes varying between 1 and 10 μV. In 5 patients no scalp HFO events could be detected. In 15 patients the ripple rate was highest over the side of the implantation and in 12 patients the highest rates were also specific to the SOZ. Ripple rates were significantly higher over the SOZ (0.4 ± 1.1 R/min) than

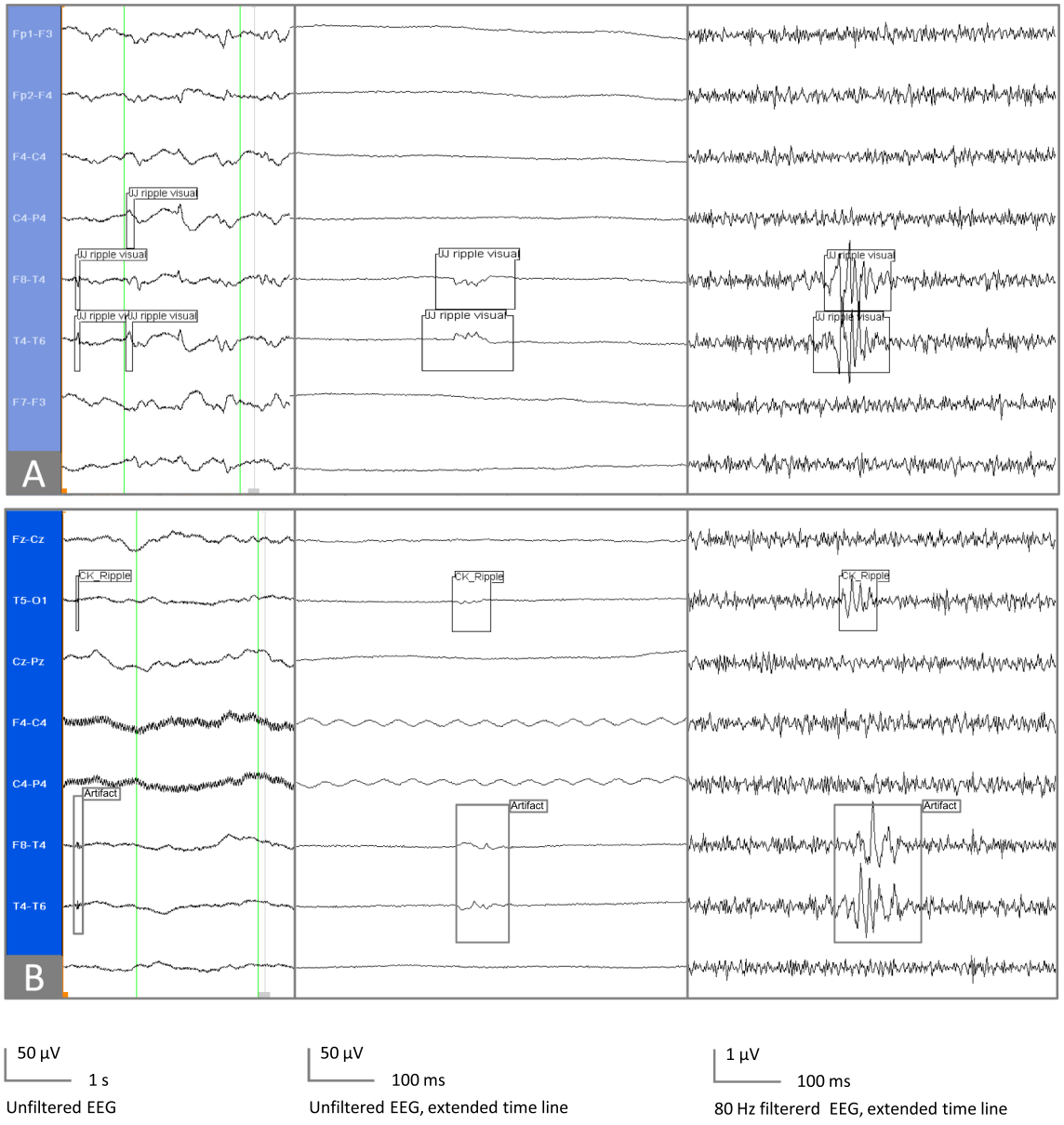

Fig. 1. Example of a spike-associated ripple with a typical amplitude (Panel A) as well as an artifact (Panel B) in the unfiltered surface EEG, with extended time line and 80 Hz filtered EEG. Please note that we rejected the oscillatory event in channel T5-O1 (Panel B) because of the simultaneous co-occurrence with the artifact and hence the impossibility to exclude a filtering phenomenon.

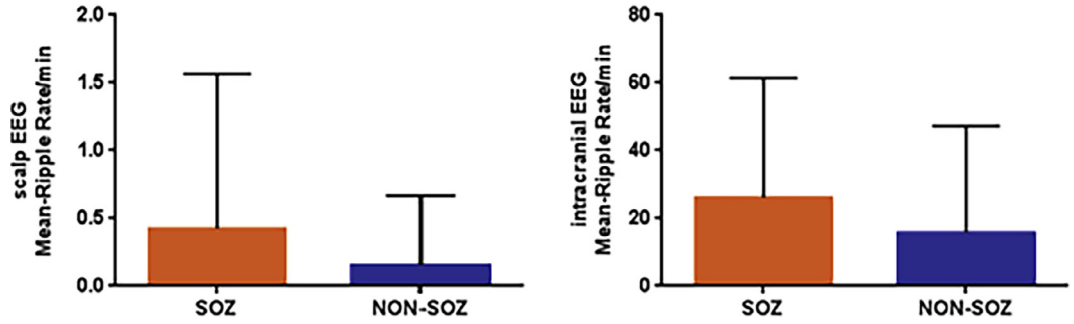

Fig. 2. Significant differences between Ripple rates in the seizure onset zone (red) and outside (blue). On the left results for the intracranial EEG and on the right results of the simultaneous scalp EEG recordings. Please note that scale on the y-axes had to be chosen differently as rates of HFOs on scalp EEG are much lower than in intracranial recordings. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

contralateral to it (0.2 ± 0.5 R/min, p = 0.03). 11 of these patients showed also ripples on the contralateral side. In three patients highest ripples rates were seen contralateral to the SOZ. Details on individual patients are given in Table 2.

3.2. Spike occurrence in scalp EEG

In 15 patients spikes were identified in the scalp EEG (10 minute segment). In 5 patients the highest spike rates were seen over the implanted hemisphere, also hosting the SOZ. In 4 patients highest spike rates were recorded from the hemisphere contralateral to the SOZ and in six patients, equal spike rates were recorded from both hemispheres. On average, spikes rates were higher over the hemisphere hosting the SOZ (1.1 ± 2.6 events/minute) than over the contralateral hemisphere (0.5 ± 1.0 events/minute, p = 0.05). Details on individual patients are given in Table 2.

3.3. Comparison of scalp and intracranial ripples

Of those 15 patients in whom the highest scalp HFO rates were found over the implanted hemisphere, the highest rate of scalp HFO was seen over the same brain region as the highest rate of intracranial HFO in 13 patients. In the two remaining patients highest rates of scalp HFO were recorded from a different lobe than highest rates of intracranial HFO. Of three patients in whom the highest ripple rate was found contralateral to the hemisphere of

Table 2
Distribution of events (10 min. of scalp EEG).

	Spikes			Number of channels	Ripples			Number of channels
	ipsilateral	SOZ	contralateral		ipsilateral	SOZ	contralateral	
1	+	+	+	7	-	-	-	0
2	-	-	+	1	-	-	-	0
3	++	++	+	4	++	++	+	3
4	+	+	-	4	+	+	++	9
5	-	-	-	0	-	-	-	0
6	-	-	-	0	++	+	+	16
7	-	-	-	0	++	++	+	10
8	+	+	+	18	+	+	+	14
9	-	-	-	0	-	-	+	1
10	-	-	-	0	-	-	-	0
11	-	-	-	0	+	+	-	1
12	+	+	+	13	+	+	-	2
13	+	+	++	6	++	++	+	8
14	-	-	+	1	+	-	+	6
15	+	+	+	6	++	++	+	8
16	++	++	+	15	++	++	+	13
17	++	++	+	13	+	-	-	1
18	+	+	-	1	++	++	+	3
19	-	-	-	0	+	-	+	8
20	-	-	-	0	+	+	-	2
21	+	+	+	3	++	++	+	12
22	-	-	+	2	++	++	+	6
23	-	-	-	0	++	++	+	4
24	+	-	+	2	-	-	-	0

Abbreviations
++ highest rate above 2/min, + HFOs present, SOZ = seizure onset zone, ipsi-/contralateral = refers to Implantation side, red = highest rate contralateral, green = highest rate ipsilateral.

the SOZ, only one had also ipsilateral ripples and this patient displayed bilateral HFO also in intracranial EEG.

3.4. Spike associated HFO

During the 10 minute period of scalp EEG, 30 % (±23%) of HFO co-occurred with spikes, ranging from 0% (no spikes in scalp EEG during that time period) to 100% (no HFO independent of spikes). In the analysis of the 1 hour scalp EEG segment, spikes were found in 23 patients, so in additional 8 patients compared to analysis of the shorter segment. In 12 of these patients associated ripples could be identified and were found in an average of 41.3% of the analyzed spikes. The spike-associated ripples were found over the same areas as in the short segment in 10 patients, in 7 patients additional ripple generating areas could be found with this method. In 10 of the patients, spike-associated ripples were found directly over the SOZ.

3.5. Comparison between postsurgical seizure outcome and scalp HFO

18 patients underwent resective surgery after implantation. 12 months post-operative seizure outcome was Engel I in 7 and Engel II-IV in 11 patients. In patients with seizure freedom 29% ± 25% of areas with scalp ripples were removed, in patients with poor outcome only 18% ± 35%. The extent of areas showing scalp HFO was significantly higher (6.1 ± 6.4 channels on average) in patients with poor seizure outcome than in those with good seizure outcome (2.4 ± 2.8 channels on average, $p = 0.02$). The comparison is given in Table 3, Table 2 gives details on the single patient level. Figs. 3 and 4 give examples of the typical distribution of HFO in patients with good and poor outcome. Additionally, all patients which did not undergo surgery had bilateral scalp ripples (see Fig. 5 for a typical example).

4. Discussion

In the current study scalp HFO could be identified in the majority of patients during simultaneous scalp and intracranial EEG recordings. As previously described, rates of scalp HFOs were much lower than in the intracranial EEG. In many patients scalp HFOs occurred over the same region as intracranial HFOs and were significantly linked to the seizure onset zone. Additional information might be added by the analysis of scalp HFOs as patients in whom HFOs occurred over more widespread brain areas had worse seizure outcome than those with more focal scalp HFOs.

A relationship between epilepsy and HFO has been shown first in micro- and then in macro-electrode intracranial recordings (Staba et al., 2002; Jirsch et al., 2006). Rodent studies suggested that the generators of HFOs are very small and it was therefore unlikely that HFOs could be seen on scalp EEG (Bragin et al., 1999a). Nevertheless scalp EEG studies suggested high frequency content in the scalp EEG which was associated with epilepsy (Wu et al., 2008; Kobayashi et al., 2009). Andrade-Valenca and coworkers also identified distinct HFO over the SOZ in clinical EEG recordings (Andrade-Valenca et al., 2011). Earlier data from our group using simultaneous scalp and intracranial EEG recordings could prove that scalp HFO have an intracranial correlate (Zelmann et al., 2013). Scalp HFO have been proposed as biomarkers for epilepsy in children with tuberous sclerosis complex (Bernardo et al., 2018). Furthermore, it has been shown that scalp HFOs in children can be used to monitor treatment success as well as estimate prognosis of genetic epilepsy (Kobayashi et al., 2011, 2015). The identification of HFOs on the scalp opens up the use of HFOs as a biomarker for epilepsy not only to a much broader patient population but also overcomes the spatial limitations of intracranial EEG. In patients with refractory epilepsy the current results suggest that scalp HFO might add information about the network and extent of epileptic activity. In the majority of patients and most prominently in those with a seizure free postsurgical outcome HFOs were most frequent over the area of implantation and the SOZ. In contrast, patients who failed to have a focal seizure onset and therefore did not undergo surgery and those with poor post-surgical outcome had more extensive HFO networks and more often bilateral HFO, suggesting that analysis of scalp HFO could yield valuable information to help predict good candidates for epileptic surgery as well as the post-surgical seizure outcome. A final conclusion on whether scalp HFO extent and postsurgical outcome are correlated would need a study with a larger number of patients and a prospective approach, but the current data certainly suggests that analysis of scalp HFOs in simultaneous recordings can add clinical information in the presurgical evaluation of patients with refractory epilepsy.

Additionally the epileptic spikes were seen in fewer patients, less conclusive, and more often bilateral. It has been hypothesized that as the skull does not have a frequency dependent transfer function the visibility of signals in the scalp EEG depends on the power of the source (Oostendorp et al., 2000) so that only spikes with a very large generator are visible on the scalp EEG (Tao et al., 2005, 2007). This might explain the few spikes seen in this study. Another explanation might be that while the depth electrodes used in stereo EEG do not significantly affect the electric potential distribution (von Ellenrieder et al., 2012b), the use of subdural grid contacts might additionally alter scalp EEG signals (Ball et al., 2009). HFO in contrast seem to be less effected by the skull and grid and are visible on the scalp even if their generators are more focal (Zelmann et al., 2013; von Ellenrieder et al., 2014). It might therefore be possible that HFO are easier to identify in simultaneous scalp EEG than spikes. Burnos and colleagues proved that HFO occurring with SEP (somato sensory evoked potential) are possible to be detected in scalp EEG and found signal attenuation along contacts of simultaneous recorded ECoG (Elecrocorticogram) a good estimator of the area contributing to a HFO (Burnos et al., 2015). Nevertheless simultaneous EEG recordings also have some disadvantages for the analysis of scalp HFO.

First, for ethical-practical reasons the number of placed electrodes is limited. Studies with simultaneous recordings and simulated data suggest that high density EEG might increase the number of visible HFO (von Ellenrieder et al., 2012a; Zelmann et al., 2013; von Ellenrieder et al., 2014). A high density EEG, as often used in the non-invasive presurgical evaluation of patients (Lantz et al., 2003; Brodbeck et al., 2011) might therefore allow to define areas of scalp HFO even more precisely and it might be that we missed some HFO generating areas in the current study.

Second, recording quality of simultaneous scalp EEG might be reduced in comparison to the separate clinical EEG recordings. In the current study, data from the first night of EEG recordings was selected to have the best impedances but electrode contacts might still be worse than in a setting in which access to electrodes is not limited by the head bandage. An even better solution for the recording of HFO might be the use of subdermal electrodes as suggested by Pizzo et al. (2016). The latter group also analyzed fast

Table 3
Extent of scalp HFO and postsurgical seizure outcome.

Outcome Engel	1	2–4
Number of patients	7	11
Unilateral HFO	29%	18%
≤4 channels	4	3
>4 channels	1	5
No HFO	2	3
# of channels with HFO	2.43	6.0

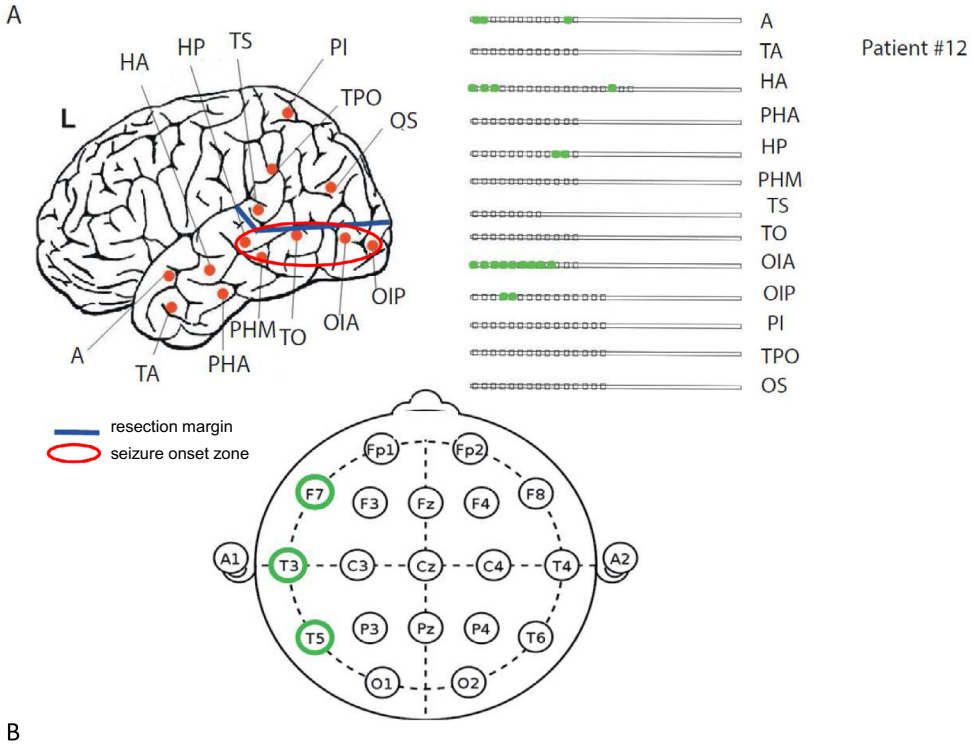

Fig. 3. Example of patient 12 with focal scalp HFO ipsilateral to the seizure onset zone and a seizure free postsurgical outcome. On the MRI the patient had an FCD located temporo-basal and occipital on the left side. He underwent a resection of the FCD as well as the mesio-temporal structures. Panel A shows the intracranial investigation and indicated areas with high HFO rates (green contacts) as well as the extent of the surgical resection. Panel B illustrated the areas of HFO occurrences in the scalp EEG (green contacts). Abbreviations: A: amygdala, HA: hippocampus, HP: posterior hippocampus, PI: Parietal, PHA: anterior parahippocampus, PHM: medial parahippocampus, OIA: occipital inferior anterior, OIP: occipital inferior posterior, OS: occipital superior, TA: temporal anterior, TO: Termporal-occipital, TPO: temporal-parietal-occipital, TS: temporal-superior. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

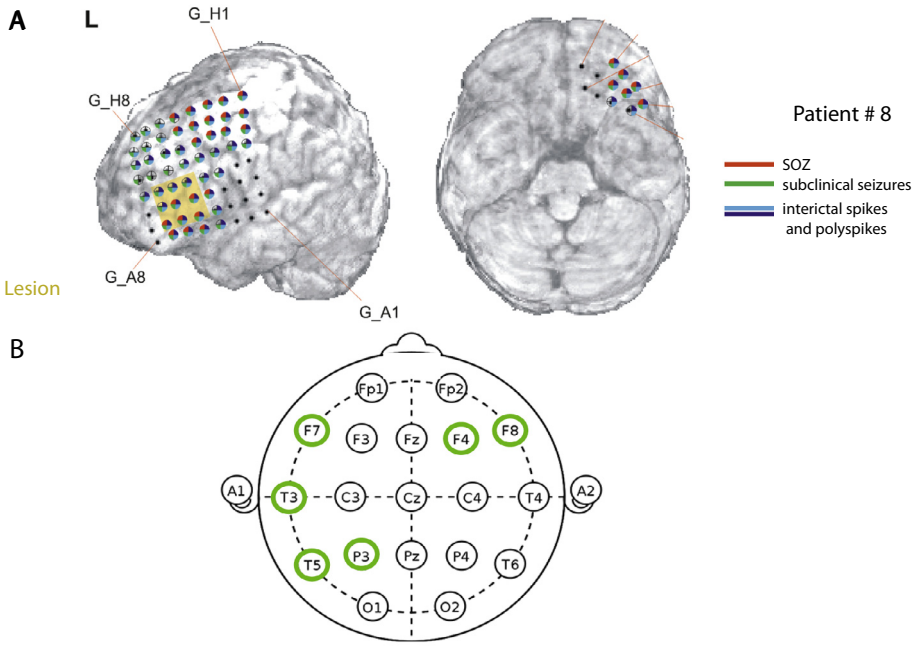

Fig. 4. Example of patient 8 with more widespread scalp HFO which do not match with the focal seizure onset zone and were seen over widespread areas. The patients underwent a lesionectomy which revealed FCD type 1. He remained to have seizures and had a post-operative seizure outcome classified as Engel 3. Panel A shows the intracranial investigation indicating the area of the lesion and seizure onset. Panel B illustrates the areas of HFO occurrences in the scalp EEG (green electrodes). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

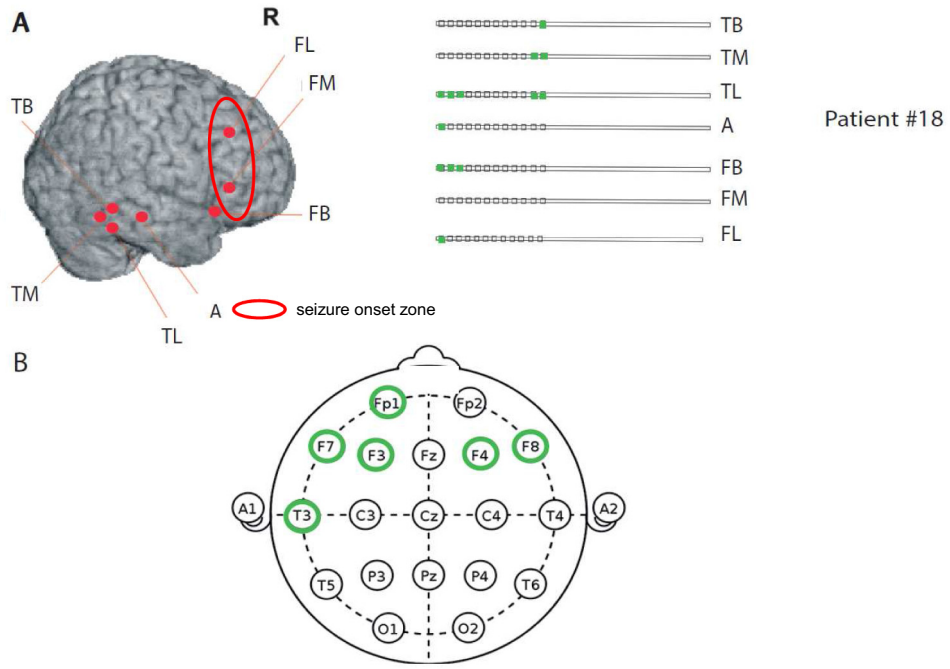

Fig. 5. Example of patient 18 with widespread scalp HFO. This patient had seizures from several seizure onset zones during the intracranial investigation including temporal and frontal areas as well as areas not contralateral to the implantation and therefore was not considered suitable for a surgical intervention. Panel A shows the intracranial investigation indicating the areas with intracranial HFO (green electrodes) Panel B illustrates the areas of HFO occurrences in the scalp EEG (green electrodes). Abbreviation: A: amygdala FB: fronto-basal,FL: fronto-lateral,FM: fronto-mesial, TB: temporo-basal, TL: temporo-lateral, TM: temporo-mesial. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

ripples with these electrodes, which as we know from intracranial EEG studies might be even more closely linked to epileptic areas. In our study we limited the analysis to ripples as this has been the mean frequency described in scalp HFO analysis previously (Andrade-Valenca et al., 2011; van Klink et al., 2016).

Subdermal electrodes might also reduce the occurrences of interfering high frequency artifacts. Another method of minimizing background noise interfering with HFO detection in scalp EEG might be implementation of low noise amplifiers as described in (Waterstraat et al., 2015; Fedele et al., 2017a). It is especially important to ensure that artifacts in the filtered EEG are not misinterpreted as HFO (Bénar et al., 2010). In the analysis of scalp EEG it is very important to be selective in the identification of HFO to make sure to exclude events which result from ringing of EEG spectral analysis and filter artifacts. We addressed this using the methods previously (Andrade-Valenca et al., 2011). Most importantly we analyzed the quality of the unfiltered EEG carefully and used FIR filters to reduce the likelihood of ringing in the filtered EEG.

Artifacts as well as the small amplitude of scalp HFO are another challenge when using HFO in a clinical setting. Automatic detectors for scalp HFOs have low sensitivity and specificity and depend on visual confirmation of scalp HFO (von Ellenrieder et al., 2012a). This is especially problematic as the low rate of scalp HFOs might require the analysis of longer EEG segments to obtain valuable results. In the current study only a short EEG segment was analyzed and as a result some areas generating HFO might be overlooked. Data from intracranial EEG suggest that HFO localization stays quite stable over time (Zelmann et al., 2009; Dümpelmann et al., 2015). Rates might vary with sleep stages but the relative differences in HFO rates between regions stay the same (Bagshaw et al., 2009). Furthermore, a recent study found very stable HFO-rates during Slow wave sleep over several days (Fedele et al., 2017b). This suggests that the areas with frequent HFOs can be identified even in shorter EEG segments, as were used for analysis in the current study. Our analysis of spike associated HFOs over one hour also showed HFO over the same brain regions as the analysis of the shorter segment. Analysis of co-occurrence between spikes and HFO may be easier in clinical routine as the identification of epileptic spikes and co-occurring HFOs is much faster than identification of HFOs only. Most importantly spikes with HFO seem to be more specific to epilepsy than spikes without HFO (Kobayashi et al., 2010). Melani and coworkers also suggest that HFOs are more common in regions which show epileptic spikes (Melani et al., 2013). Therefore screening EEGs for the occurrence of spikes might be used as a preselection for EEG contacts which are interesting for HFO analysis. In addition, analysis of a longer EEG segment for the detection of spikes – although in this condition HFO not co-occurring with spikes may be missed – may yield additional valuable information regarding the epileptic network.

Our data suggest that some HFOs occur in channels without any epileptic spikes and that these HFOs also might be of clinical value and those HFO might be missed if the EEG is not analyzed with an extended time line and independently of the occurrence with spikes. The future of analyzing scalp HFOs might therefore be an improved automatic detection as well as a more detailed analysis of spikes. However, the development of automatic detectors for HFO in surface EEG is challenged by several factors. Even if the lower signal to noise ratio can be overcome as described above by subdermal electrodes and low noise amplifiers, there remains the problem that inter-rater reliability of visually detected scalp-HFO can be poor (Gardner et al., 2007) and hence a gold standard is lacking to validate future automatic detectors. For iEEG data in this study the average kappa between visual and automatic markings for all channels and patients was 0.62 ± 0.12. Average kappa of scalp EEG data between the two reviewers was 0.58 + 0.8, this however did not influence the data of the study as for scalp EEG

we only accepted events marked by both reviewers (CK and JJ), thus creating an inter-rater reliability of 100% on the one hand but accepting on the other hand that some HFO might have been falsely rejected. To overcome this problem and validate future automatic detecting procedures, a consensus is needed in the research community which defines morphology and frequency characteristics of scalp HFO in more detail.

In this study, we did not analyze iEEG spikes and co-occurrent HFO as this topic has been addressed previously (Pail et al., 2013; Wang et al., 2013; Jacobs et al., 2016), but we analyzed scalp spikes in order to ensure that events counted as scalp HFO were not filtering artifacts of spikes.

For EEG recording (intracranial as well as scalp EEG) we used a sampling rate of 2000 Hz and a low pass filter of 800 Hz as these parameters were pre-implemented in our EEG setting. According to the IFCN Guidelines of 1999 on frequency analysis of EEG low pass filter of 500 Hz would have been preferable to remove aliasing. However, because of the steepness of the filter, there are no significant reflexions at 1998 Hz that could interfere with the detection of slow wave sleep. We therefore assume that our analysis at 2 Hz for sleep staging as well as our analysis of high frequencies (HFO) are not biased by filtering effects. In future, a higher sampling rate might also contribute to an even more accurate reconstruction of the EEG signal.

In our study, the patient cohort is relatively small. However, as in our Epilepsy Centre, all patients routinely receive scalp EEG in addition to intracranial EEG we were able to recruit consecutive patients for our study, thus avoiding a selection bias regarding the spectrum of epileptic pathologies. Therefore, albeit small, our cohort can be considered representative for the spectrum of patients with pharmacoresistant epilepsy.

Data from our group has proven co-occurrence between scalp and iEEG HFO in the past (Zelmann et al., 2013). Analyzing coupling and frequency correlation between scalp and iEEG events is not trivial as some depth contacts like in this study might be far away from the scalp. This study therefore cannot provide information about the co-occurrence of events but was restricted to analyzing whether events occurred over the same brain lobe.

In conclusion, the current study confirms that scalp HFOs can be seen in simultaneous scalp and intracranial EEG recordings. Scalp HFOs are closely linked to areas of seizure onset but might also occur more widespread and then indicate a larger epileptic network. Analysis of high density scalp EEG prior to implantation as well as of larger number of patients would be necessary to confirm the clinical value of scalp HFOs in a presurgical setting.

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Conflict of interest statement

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

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