BRAIN COMMUNICATIONS

Stable high frequency background EEG activity distinguishes epileptic from healthy brain regions

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High-frequency oscillations are markers of epileptic tissue. Recently, different patterns of EEG background activity were described from which high-frequency oscillations occur: high-frequency oscillations with continuously oscillating background were found to be primarily physiological, those from quiet background were linked to epileptic tissue. It is unclear, whether these interactions remain stable over several days and during different sleep-wake stages. High-frequency oscillation patterns (oscillatory vs. quiet background) were analysed in 23 patients implanted with depth and subdural grid electrodes. Pattern scoring was performed on every channel in 10 s intervals in three separate day- and night-time EEG segments. An entropy value, measuring variability of patterns per channel, was calculated. A low entropy value indicated a stable occurrence of the same pattern in one channel, whereas a high value indicated pattern instability. Differences in pattern distribution and entropy were analysed for 143 280 10 s intervals with allocated patterns from inside and outside the seizure onset zone, different electrode types and brain regions. We found a strong association between high-frequency oscillations out of quiet background activity, and channels of the seizure onset zone (35.2% inside versus 9.7% outside the seizure onset zone, $P < 0.001$), no association was found for high-frequency oscillations from continuous oscillatory background ($P = 0.563$). The type of background activity remained stable over the same brain region over several days and was independent of sleep stage and recording technique. Stability of background activity was significantly higher in channels of the seizure onset zone (entropy mean value 0.56 ± 0.39 versus 0.64 ± 0.41; $P < 0.001$). This was especially true for the presumed epileptic high-frequency oscillations out of quiet background (0.57 ± 0.39 inside versus 0.72 ± 0.37 outside the seizure onset zone; $P < 0.001$). In contrast, presumed physiological high-frequency oscillations from continuous oscillatory backgrounds were significantly more stable outside the seizure onset zone (0.72 ± 0.45 versus 0.48 ± 0.53; $P < 0.001$). The overall low entropy values suggest that interactions between high-frequency oscillations and background activity are a stable phenomenon specific to the function of brain regions. High-frequency oscillations occurring from a quiet background are strongly linked to the seizure onset zone whereas high-frequency oscillations from an oscillatory background are not. Pattern stability suggests distinct underlying mechanisms. Analysing short time segments of high-frequency oscillations and background activity could help distinguishing epileptic from physiologically active brain regions.

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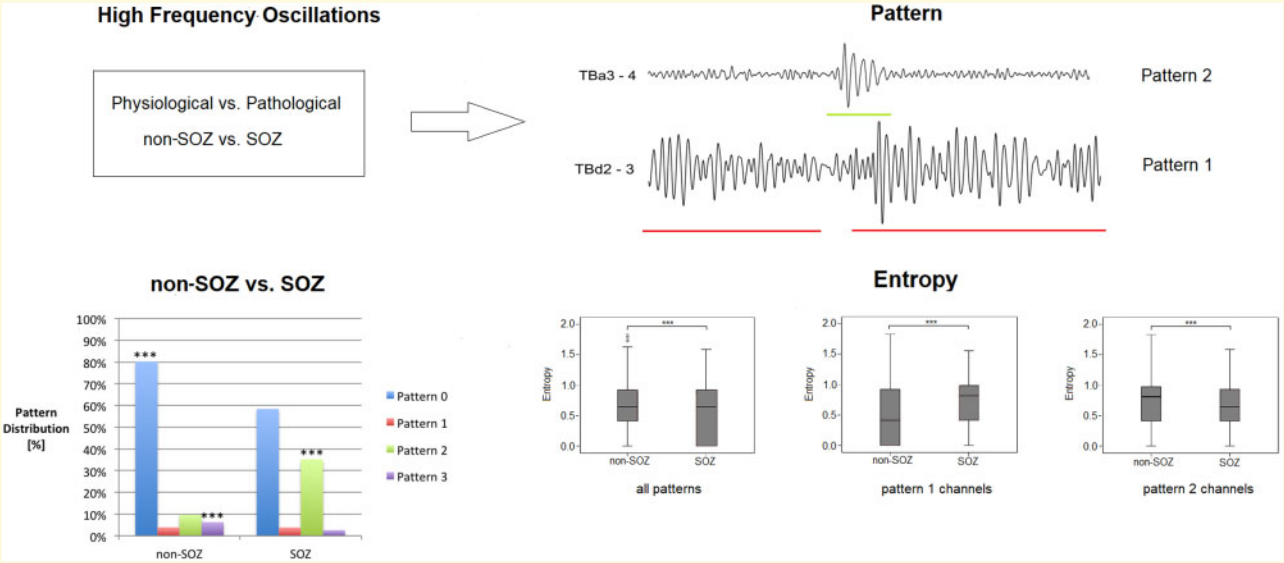
Graphical Abstract



Abbreviations: APE = average pattern entropy; HFO = high-frequency oscillations; SOZ = seizure onset zone

Introduction

Over the last 20 years high-frequency oscillations (HFO) became a promising marker of epileptogenicity in the human brain. They consist of at least four consecutive oscillations clearly standing out from the baseline EEG (Zelmann *et al.*, 2009). With regard to its length, the definition of HFO varies: in the early literature HFO were generally defined as very short events (20–100 ms). More recently, different lengths of HFOs have been described (Zijlmans *et al.*, 2017). Furthermore, they can be divided by their frequency range into ripples (80–250 Hz) and fast ripples (250–500 Hz) (Bragin *et al.*, 1999*a*).

Originally, HFO were recorded from microelectrodes that were used for research purposes (Bragin *et al.*, 1999*b*). A few years later, it could be shown that they can also be recorded with clinical macroelectrodes (Jirsch *et al.*, 2006; Urrestarazu *et al.*, 2007). The described fast oscillations seem to be more specific to the seizure onset zone (SOZ) than traditional spikes (Jacobs *et al.*, 2008; Cho *et al.*, 2012). The surgical removal of HFO correlated with post-surgical seizure outcome in several retrospective studies (Ochi *et al.*, 2007; Wu *et al.*, 2010; Akiyama *et al.*, 2011; Nariai *et al.*, 2011; Frauscher *et al.*, 2017). Nevertheless, some studies could not support this correlation (Haegelen *et al.*, 2013; van't Klooster *et al.*, 2017; Jacobs *et al.*, 2018) and a very recent study suggests that the identification of epileptic areas with HFO might be complicated in individual patients (Roehri *et al.*, 2018). One reason for the failed correlation might be the inability to successfully differentiate between physiological and epileptic HFO (Jacobs *et al.*, 2016).

Over the past few years, many studies focused on the differentiation between physiologic and pathologic HFO (Frauscher *et al.*, 2017). First investigations on HFO hypothesized that fast ripples reflect pathologic oscillations whereas ripples represent physiological events that are important for memory consolidation (Buzsáki and Chrobak, 1995). Later, it was shown that frequency alone is not sufficient for separating these two types of oscillations (Engel *et al.*, 2009). Both, fast ripples and ripples, can be detected in epileptic as well as in normal brain regions (Hashimoto, 2000; Gobbelé *et al.*, 2004; Worrell *et al.*, 2008; Jacobs *et al.*, 2009).

Some groups therefore investigated HFO features such as amplitude and duration (Nagasawa *et al.*, 2012; Alkawadri *et al.*, 2014). Others focused on different phase-coupling of physiological and pathological oscillations with slow waves during sleep (Frauscher *et al.*, 2015; von Ellenrieder *et al.*, 2016) or sleep spindles (Bruder *et al.*, 2017). One interesting finding with regard

to this question was the changes in EEG-baseline activity found while visually analysing HFO in depth electrodes (Melani *et al.*, 2013). To further characterize this new finding in the ripple band, Melani and coworkers defined and analysed three types of HFO pattern: Pattern 1 was described as channels presenting a background occupied by a continuous or semi-continuous HFO activity; Pattern 2 was characterized by a type of background presenting infrequent short-duration oscillations and pattern 3 was described as an irregular EEG activity with irregular duration of HFO. The study found no correlation between the continuous oscillating pattern and the SOZ, concluding that this pattern might be an intrinsic physiologic characteristic of specific brain regions (Melani *et al.*, 2013). Almost at the same time, Kerber *et al.* (2014) investigated HFO patterns in patients implanted with neocortical grid electrodes and made similar findings: surgical resection of ripple pattern in a continuous background was not significantly associated with postsurgical outcome, whereas removal of areas with pattern 2 was. Moreover, in contrary to the highly time consuming marking of single HFO events, pattern scoring was suggested to be a potentially new and faster way of assessing HFO activity.

Both studies on HFO pattern were limited to analyses of short slow-wave-sleep EEG-segments. Changes of HFO pattern over a longer period of time have not been investigated yet. However, HFO pattern stability is of great interest and is necessary for the clinical use of patterns (Melani *et al.*, 2013; Kerber *et al.*, 2014). High HFO pattern stability would support the notion that HFO patterns reflect a stable underlying mechanism. Especially in clinical settings, it is indispensable to know whether background patterns are a stable phenomenon that provides reliable information about potentially epileptic regions.

We hypothesize that HFO patterns reflect the brain's capacity to generate physiological or epileptic oscillations and therefore remain stable over the same brain regions independent of sleep stage or wakefulness. As a result, a short analysis of patterns during the first EEG period might be sufficient to improve SOZ localization in patients with refractory epilepsy.

Material and methods

Patient selection

Consecutive patients were included who underwent intracranial recordings in the Epilepsy Center Freiburg, Germany, due to pharmaco-resistant epilepsy between February 2011 and December 2014 with the following inclusion criteria:

At least one mesiotemporally placed electrode and the possibility to find artefact-free intervals with at least 2 h of seizure-freedom before and after the selected segment, plus a sampling rate of 2000 Hz.

All patients gave informed consent to participate in this study. The study was approved by the local ethics committee.

EEG-recordings and selection of segments

All of our retrospectively analysed EEG data were recorded by three types of electrodes: subdural grid electrodes (32 or 64 contacts), strip electrodes (4 or 6 contacts) or depth electrodes (5–8 contacts). All contacts were produced by AD-Tech (AD-TECH Medical Instrument Corporation, Racine, WI, USA). Intracranial EEGs were recorded with the software 'Profusion' (Compumedics limited, Abbotsford, Victoria), a sampling rate of 2000 Hz and a low pass filter of 800 Hz. In order to analyse the changes of HFO over a longer period of time, we selected three night-time and three day-time EEG segments of 2 min each for every patient. Due to more frequent occurrence of HFO during slow-wave-sleep (Bagshaw *et al.*, 2009), the deepest sleep-stage found per night was included in the study. We tried to analyse every other night and day. With regard to the daytime-epochs, we did the same, selecting only segments of wakefulness with a temporal distance of at least 2 h from any seizure.

Pattern analysis

After highpass-filtering the intracranial EEG with 80 Hz, patterns were visually marked using the Harmonie system (Stellate, Montréal, Canada) and a bipolar montage. The intracranial EEG was displayed with the maximum time resolution. The maximum time resolution available was 0.8 s/page so that 800 ms of EEG were visible on the computer screen at one point in time.

Visual classification into patterns 0, 1, 2 and 3 was conducted as described by Kerber *et al.* (2014): Patterns were defined by visual criteria such as the difference in amplitude between oscillations and baseline EEG activity, the length of HFO and a clear separation between HFO and non-oscillatory baseline activity.

Pattern 0: no HFO/oscillatory activity. Pattern 1: background almost completely occupied by a continuous/semi-continuous oscillatory activity with HFO like activity lasting >500 ms. Pattern 2: pattern with sporadic oscillations with a duration up to 200 ms that are clearly separable from baseline activity. Pattern 3: scored when a mixture between the other patterns occurred and no clear classification was possible. This mostly occurred if longer oscillatory activity like in pattern 1 was observed but then interrupted by non-oscillatory activity (see channel LI 1–2 in Fig. 1). In some channels, oscillatory activity that was different from flat line of pattern 0 but not meeting criteria for HFO was observed as demonstrated in channel OI8–9 in Fig. 1. This as well was classified as pattern 3. A characteristic example for each pattern is shown in Fig. 1.

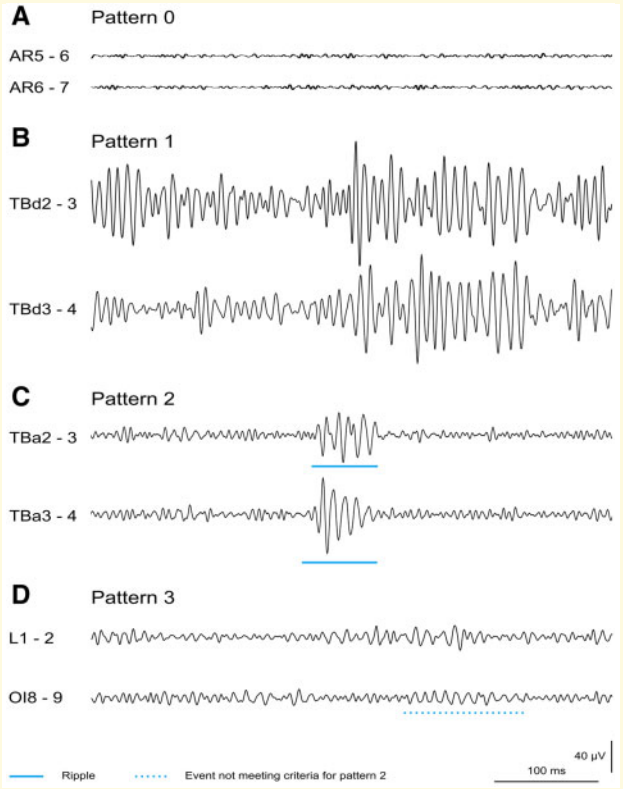


Figure 1 Characteristic examples for each pattern. (**A**) Pattern 0 with no HFO activity. (**B**) Pattern 1 with a background almost completely occupied by a continous/semicontinuous oscillatory acitivity. (**C**) Pattern 2 with sporadic short HFO out of a flat baseline activity. (**D**) Pattern 3 as irregular pattern.

Each 2 min segment of every channel was manually analysed separately. To investigate the stability of the pattern, we conducted the classification into the four different patterns in 10-s intervals for each channel segment. With regard to pattern allocation, the dominating pattern within the 10-s interval was chosen. Thus, a value for one of the four patterns was allocated 12 times within each 2 min segment for each channel.

In order to evaluate the specificity of each pattern in predicting the SOZ, we compared pattern rates and their correlation with SOZ/non-SOZ channels. Pattern probabilities were calculated for patterns 1, 2 and 3 for each channel segment. In our analysis, pattern probability could reach values from 0 to 1, indicating no and exclusive presence of the analysed pattern, respectively.

Entropy analysis

In order to evaluate the stability of the visually marked pattern, entropy was computed based on the patterns in each channel. Entropy can be used as a measure of stability of a value during several repetitive measurements. We therefore used entropy to assess the variability of the HFO pattern: It refers to the order or disorder with which the mentioned patterns occur within a channel and during 2 min, i.e., the order or disorder with which the four patterns occur in the 12 time segments within each channel. In our analysis, entropy could reach values from 0 to 2. A low value indicates a frequent and therefore stable occurrence of the same pattern in one channel, whereas a high entropy-value indicates instability and therefore low predictability of the occurrence of the patterns. Examples of frequently used entropy values and possible pattern distribution shown in Fig. 2.

In a first step, an entropy value was calculated for each channel including the allocated patterns of 12 time segments to compare differences in entropy between mesiotemporal and neocortical channels, SOZ and non-SOZ as well as grids and depth electrodes.

In a second step, we computed a separate entropy value for the day- and night-time segments of every channel in order to compare differences between wakefulness and sleep over time. For this investigation, the entropy value was calculated including the allocated patterns of 36 time segments.

Any of the described patterns were not circumscribed to a single group of channels. Therefore, the dominance of each pattern within a channel was determined manually. If within a 2 min segment a certain pattern was allocated in at least 50% within the respective channel, this pattern was classified as dominant. Analysing the pattern-entropy of the channels with a given pattern-dominance allowed quantifying the stability of the dominating pattern across the 2-min segments.

For this reason, the average pattern entropy (APE) and the standard deviation were calculated across those channels which showed dominance of one of the described patterns (i.e. a given pattern occupying 50% or more of the 2 min analysed). The APE was used to analyse if the pattern was very stable over the 2 min (low APE) or rapidly alternated with other patterns (high APE).

Statistical analysis

For the statistical analysis, contacts were defined as inside or outside the SOZ, mesiotemporal or neocortical contacts, subdural or depth electrodes and wakefulness or sleep. The SOZ was defined individually for every patient by experienced neurologists as channels showing the earliest ictal EEG-changes. Information about electrode localization, type of electrodes and circadian state was obtained from patient records and MRI after electrode implantation.

In a first analysis, a chi-square test was used to compare the distribution of the different patterns between SOZ and non-SOZ channels, mesiotemporal and neocortical structures, grids and depth electrodes and episodes of sleep and wakefulness. After that, we compared the distribution of patterns between SOZ and non-SOZ

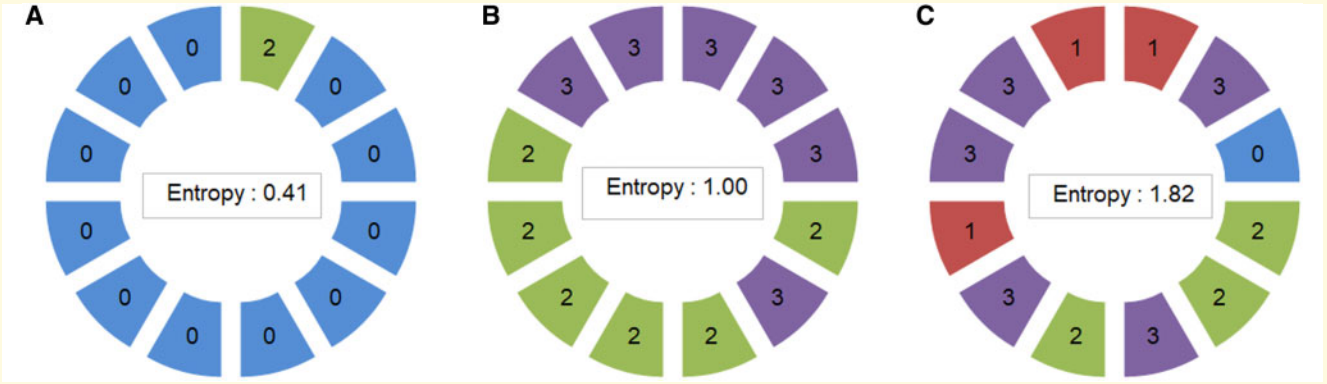


Figure 2 Examples of frequently used entropy values and possible pattern distribution.

separately just for depth electrodes and mesiotemporal brain structures.

The test was employed on a single pool including all patients' data. In a second step, we also conducted the test on an individual level.

In a second analysis, we used Mann–Whitney U-tests to compare the correlation of patterns' 1, 2 and 3 probability and SOZ/non-SOZ channels. Again, the test was employed on a single pool including all patients' data.

In a third step, a Mann–Whitney U-test was used to compare entropy values between the parameters already investigated in the first analysis. For all statistical analyses, SPSS Statistics (IBM Corporation, Armonk, NY, USA) was used. Significance level for all tests was $P < 0.05$.

Data availability

The data presented in this study, are acquired from patients and their consent refers to this specific study, therefore the data cannot be made publically available. However, if other researchers would like to use the data for research purposes, please contact the corresponding authors to get more information about how we can share the data after requesting consent.

Results

Patients and clinical data

We included 23 consecutively implanted patients in our study. All patients received stereotactic EEG-implantation, additional subdural electrodes were implanted in six patients (26%). 2089 channels were included in our analysis. Selected segments from 51 (2.4%) channels had to be excluded due to artefacts or faults. A total of 1806 (86.5%) channels were located outside the SOZ, 283 (13.5%) inside the SOZ. Of all, 206 (9.9%) channels were placed in mesiotemporal structures, 1883 (90.1%) in neocortical regions. Ten (66.7%) of 15 operated patients had a seizure-free post-surgical outcome (Engel Class 1) and five (33.3%) patients a poor postsurgical outcome (Engel Class 2–4). Information of clinical details and electrodes is presented in Table 1.

Distribution of patterns

All 2089 channels were included in this analysis. Using the methods of pattern allocation, a total of 143 280 10 s intervals with allocated patterns could be included in this analysis after excluding those patterns that derived from defective channels ($n = 7128$). Considering all channels, the distribution of the four different patterns was as follows: Pattern 0 = 77.2%, pattern 1 = 3.9%, pattern 2 = 13.1% and pattern 3 = 5.8%.

The chi-square test employed on a single pool including all patient's data showed a non-random distribution between background pattern and neocortical versus mesiotemporal brain regions [$x^2(3) = 4480.27$; $P < 0.001$] with significantly higher prevalence of patterns 1 and 2 in mesiotemporal structures whereas patterns 3 and 0 were found to have significantly higher prevalence in neocortical structures (Fig. 3A).

With regard to different electrode types also a non-random distribution was found. All patterns presented significantly higher prevalence in subdural electrodes [($x^2(3) = 27\ 667.62$; $P < 0.001$; Fig. 3C] except pattern 0, which was most often seen in depth contacts.

Concerning the sleep-wake cycle, pattern 2 was significantly more frequent in sleep, while all other patterns were most prominent during wakefulness [$x^2(3) = 1172.25$; $P < 0.001$] (Fig. 3D).

The distribution of the background pattern between SOZ and non-SOZ channels showed a non-random distribution [$x^2(3) = 9760.11$; $P < 0.001$] for all patterns except pattern 1, which showed a random distribution between SOZ and non-SOZ channels. As expected, percentage of channels with pattern 2 was significantly higher inside the SOZ than outside the SOZ (35.2% vs. 9.7%; Fig. 3B), whereas patterns 3 and 0 were found to

Table 1 Clinical details (age, gender, type of seizure, MRI/histology, surgery, outcome) and electrode information (number, type and placement) of the patients. Outcome classified according to Engel et al. (1993)

Patient no.	Gender	Age	Electrodes: number, type and placement	Type of seizure	MRI/histology	Surgery	Outcome (Engel)
1	M	50	12 DE (R-P, R-F, R-T)	SFS, CFS, GTCS,	FCD, HS	2/3 T-R Res,AHC-R	IIa
2	F	29	9 DE (L-T, R-T)	SFS, CFS, GTCS	S.o. FCD-TMA-L	–	–
3	F	17	14 DE (L-F, L-I, L-T, R-F)	SFS, CFS	FCD I-L+ Opc-F+Opc-P	–	–
4	M	35	12 DE (R-T, L-T)	SFS, CFS, GTCS	Bil HL	–	–
5	F	18	14 DE (L-F, L-T, L-I, L-CG, L-Am, L-Hc, L-EC)	SFS, CFS, GTCS	FCD TMS-L	–	–
6	F	35	13 DE (R-T, R-P, R-O, R-I)	SFS, CFS, GTCS	S.o. dyspl.Hc/Am-R	–	–
7	F	41	13 DE (L-T, R-T)	CFS, GTCS	HA-L	–	–
8	M	12	10 DE (R-F, R-T, R-I)	SFS, CFS, GTCS	FCD T-R; HS	T-R Res (incl. AHC)	IId
9	F	25	13 DE (L-T, R-T)	SFS, CFS	DVA F-R	–	–
10	F	37	6 DE (R-T, L-O, L-I)	SFS, CFS, GTCS	H.o. Res TP-R, HS	2/3 T-R Res (incl. AHC)	IIIa
11	F	17	1G (L-TP), 7St (L-TB, L- TP, L-O), 1 DE (L-Hc)	SFS, CFS	FCD L-TP, HS-L	AHC-LExt. Lesionectomy L-TP+TL	Ia
12	M	52	4 DE (L-Hc-Am, R-Hc-Am), 4 St (L-TB, L- TP), 1 G (L-TL)	SFS, CFS	Lesion L-Opc	TopectomyL-P-Opc	Ia
13	F	48	12 DE (R-T, L-TO, L-P)	SFS, CFS, GTCS	Bil HS	–	–
14	M	36	2 DE (L-Hc, L- Heschl), 1 G (L-TP), 8 St (Pre-c-L, Po-c-L, TP-L, TB-L)	SFS, CFS, GTCS	Non-lesional	MST L-TPo, L-TB	IVb
15	F	40	10 DE (R-T, L-T)	SFS, CFS, GTCS	HS-R	2/3 T-R Res (incl. AHC)	Ia
16	M	33	11 DE (R-T, R-P, R-I, R-F)	CFS, GTCS	FCD R-T, HS-R	T-R Res (incl. AHC)	Ia
17	M	25	7 DE (L-T, L-O)	SFS, CFS, GTCS	FCD-TMS-L	Lesionectomy-L (incl. dors. HC-L)	Ib
18	F	60	8 DE (L-T, R-T)	SFS, CFS, GTCS	Bil MEC-TP, Lesion L-TP	Ext. Lesionectomy-L-TP	Ib
19	F	29	11 DE (R-T, R-F, R-I)	SFS, CFS, GTCS	HS	2/3 T-R Res (incl. AHC)	Ia
20	F	42	10 DE (R-I, R-T)	SFS, CFS, GTCS	FCD TMP-R+ I-R, HS	2/3 T-R Res (incl. AHC)	Ia
21	W	25	1 DE (L-T), 1 G (L-T), 3 St (L-T)	SFS, CFS, GTCS	Lesion L-T: ganglioglioma	Ext. Lesionectomy-L-TL	Ib
22	F	52	1 DE (L-T), 1 G (L-T), 5 St (L-T)	SFS, CFS, GTCS	HS-L, S.o. FCD-Am-L	SAH-L	Ia
23	M	17	1 DE (L-T), 10 St (L-T, L-O, L- P), 1 G (L-TO)	SFS, GTCS	FCD O-L+ T-L	OP-L Res	IIa

AHC = amygdalo hippocampectomy; Am =amygdala; Bil = bilateral; CFS = complex focal seizure; CG = cingulate gyrus; DE = depth electrode; Dors = dorsal; DVA = developmental venous anomaly; EC = entorhinal cortex; Ext. = extended; FCD = focal cortical dysplasia; f = female; F = frontal; G = grid; GTCS = generalized tonic clonic seizure; HA = hippocampal atrophy; Hc = hippocampus; Heschl = Heschl's gyri; HL/- S = hippocampal lesion/ -sclerosis; H.o. = history of; Incl. = inclusive; I = insula; L = left; m = male; MEC = meningoencephalocele; MST = multiple subpial transection; O = occipital; OP = occipital pole; Opc = operculum; P = parietal; Post-c = postcentral; Pre-c = precentral; R = right; Res = resection; SAH = selective amygdala-hippocampectomy; SFS = Simple focal seizure; S.o. = suspicion of; St = strips; T = temporal; TB = temporo-basal; TL = temporo-lateral; TMA = temporo-mesial-anterior; TMP = temporomesiopolar; TMS = temporo-mesial; TO = temporo-occipital; TP = temporo-polar; TP = temporal pole; TPo = temporo-posterior.

have significantly higher prevalence outside the SOZ. Higher prevalence of pattern 2 inside the SOZ than outside the SOZ was also seen analysing only depth electrodes and mesiotemporal structures separately (Supplementary Fig. 1).

Analysing pattern distribution on an individual level we again found a non-random distribution of pattern for all analyses ($P < 0.001$). Only pattern distribution between neocortical and mesiotemporal brain regions of Patient 3 revealed a random distribution ($P = 0.952$) (Supplementary Table 1).

With regard to different electrode types, statistics could not be performed in the majority of cases/patients due to the single use of either depth or subdural electrodes.

Pattern-probability

To investigate whether the occurrence of a specific pattern is predictive for the SOZ, we calculated the pattern-probability of patterns 1, 2 and 3 for every channel segment after excluding all channel segments presenting artefacts ($n = 594$) or exclusively pattern 0 ($n = 7395$) from our analysis. A total of 4545 segments could be included in this analysis. The Mann–Whitney U-test revealed significant differences ($P < 0.001$) for all pattern-probabilities and SOZ/non-SOZ-channels with higher mean values for the probabilities of pattern 1 and pattern 3 for channels outside the SOZ compared to those inside the SOZ (0.12 ± 0.3 versus 0.06 ± 0.2; $U = 1\ 730\ 322.0$; 0.19 ± 0.31 versus 0.04 ± 0.15; $U = 1\ 350\ 853.0$). On the contrary, the probability of pattern 2 showed a higher mean value for channels inside the SOZ compared to those outside the SOZ (0.53 ± 0.36 versus 0.29 ± 0.31; $U = 1\ 085\ 085.0$).

Figure 4 shows the receiver operating characteristic curve illustrating the results of the classification of channels into SOZ or non-SOZ based on pattern probabilities. The area under the curve was 0.47 for the pattern 1-probability, 0.71 for pattern 2-probability and 0.36 for pattern 3-probability.

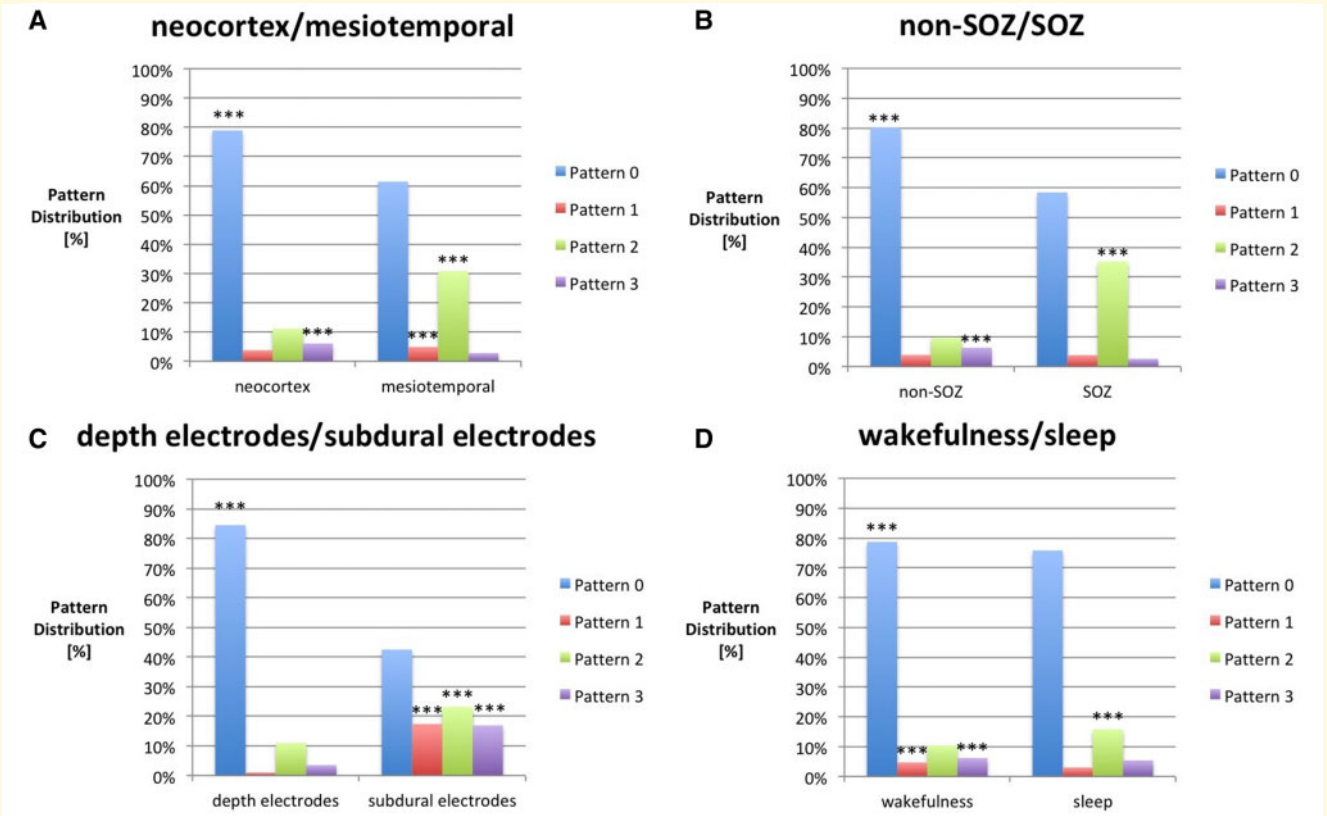


Figure 3 Distribution of patterns. Distribution of patterns in neocortex/mesiotemporal structures (**A**), non-SOZ/SOZ (**B**), depth electrodes/subdural electrodes (**C**) and wakefulness/sleep (**D**). Percentage of channels with pattern 2 is significantly higher ($P < 0.001$) inside the SOZ than outside the SOZ (**B**) and significantly higher ($P < 0.001$) in the night-time-segments than during wakefulness (**D**). Asterisks (***) indicate significant differences ($P < 0.001$) in pattern distribution.

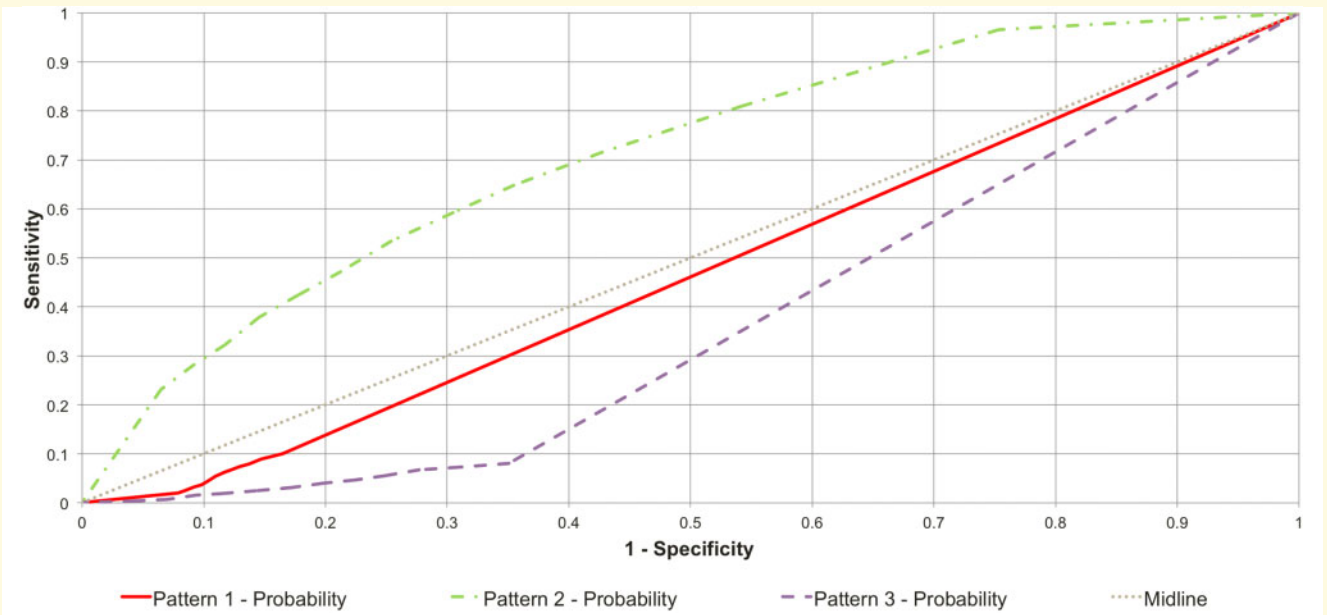


Figure 4 Receiver operating characteristic curve illustrating the results of the SOZ classification based on pattern probabilities. The area under the curve was 0.47 for pattern 1-probability (red), 0.71 for pattern 2-probability (green) and 0.36 for pattern 3-probability (purple).

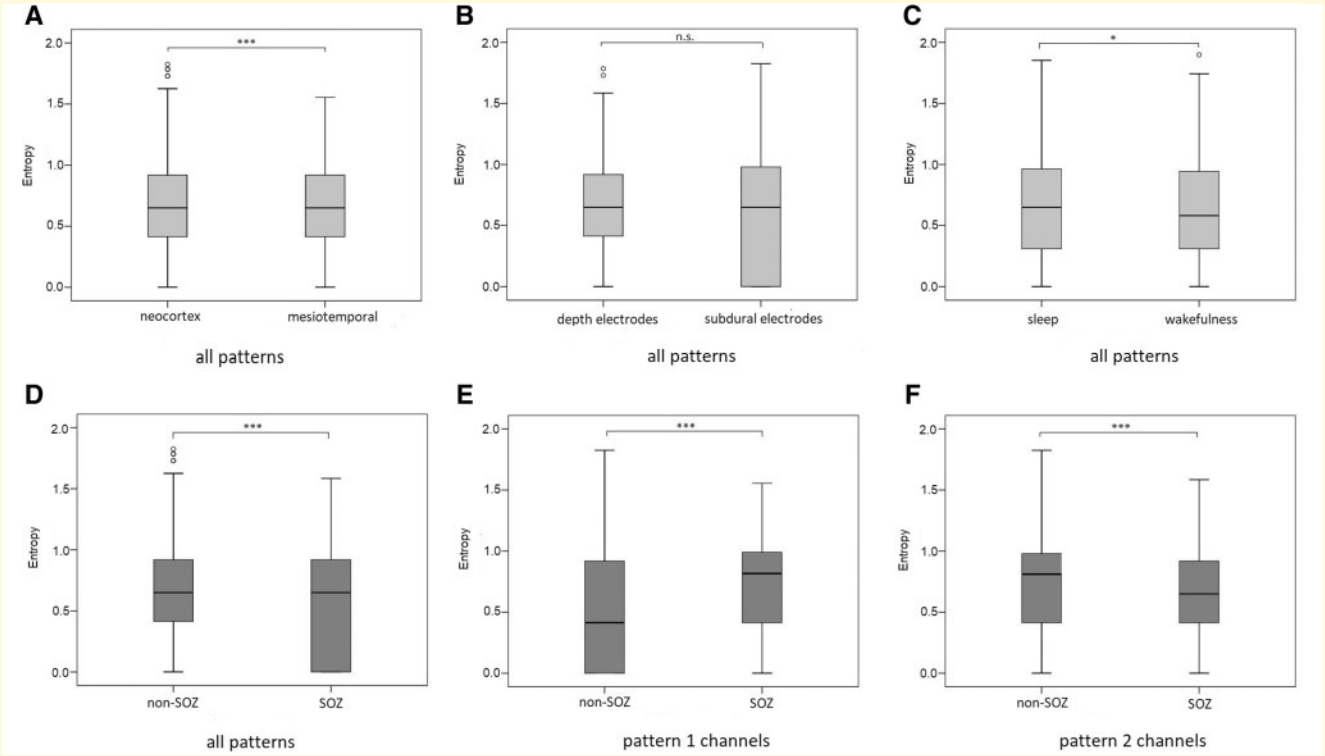


Figure 5 Boxplots illustrating differences in pattern entropy. Differences in pattern entropy between neocortex/mesiotemporal structures (**A**), depth electrodes/subdural electrodes (**B**), sleep/wakefulness (**C**), non-SOZ/SOZ: all pattern types (**D**), non-SOZ/SOZ: pattern 1 channels (**E**) and non-SOZ/SOZ: pattern 2 channels (**F**). Data within the boxes represent the 25–75% quartile, circles indicate outliers and the line in the middle shows the median value of entropy. Although statistically significant differences were found (***$P < 0.001$; * $P = 0.05$; n.s. = not significant), a large overlap with respect to entropy values can be seen in the boxplot analyses for all investigated groups with 75% of the values to be found with an entropy less than 1.

Pattern entropy

Seventy-five per cent of the entropy values were found to be less than 1 (Fig. 5), suggesting that HFO background patterns overall seem to be a stable phenomenon.

In those channels where pattern 1 was dominant, we found the lowest APE with 0.26 (standard deviation 0.39). These were followed by channels where pattern 2 was dominant with an APE of 0.49 (standard deviation 0.42). Channels with dominance of pattern 3 presented an APE of 0.64 (standard deviation 0.44) whereas those with dominance of pattern 0 revealed an APE of 0.66 (standard deviation 0.24).

After excluding artefact segments ($n = 594$) and those showing exclusively pattern 0 ($n = 7395$), in total 4545 channel segments could be included to compare differences in entropy between mesiotemporal and neocortical channels, SOZ and non-SOZ and grids and depth electrodes. In total, 2220 channel segments could be included to compare differences in entropy between wakefulness and sleep.

Analysing all pattern types, entropy was significantly lower in SOZ than in non-SOZ-channels (mean value 0.56 ± 0.39 versus 0.64 ± 0.41; $P < 0.001$; U = 1 675 364.50). Selecting only those channels with pattern 2 ($n = 3650$), significantly lower entropy in channels of the SOZ than in non-SOZ channels was demonstrated likewise (0.57 ± 0.39 versus 0.72 ± 0.37; $P < 0.001$; U = 1 092 586.0). Contrary results were found after selection of those channels presenting pattern 1 ($n = 680$), where higher entropy was found in SOZ than in non-SOZ-channels (0.72 ± 0.45 vs. 0.48 ± 0.53; U = 22 429.50). Thus, stability of patterns, specifically pattern 2, was higher in the SOZ than outside.

Entropy was significantly higher in in neocortical than in mesiotemporal regions (mean value 0.63 ± 0.41 versus 0.57 ± 0.38; $P < 0.001$; U = 1 304 106.50) and also higher during sleep than during wakefulness (mean value 0.66 ± 0.42 versus 0.62 ± 0.42; $P = 0.02$; U = 580 293.50). No significant difference in entropy was found between subdural and depth electrodes ($P = 0.76$; U = 2 304 709.50).

Discussion

The high frequency background activity of intracranial EEG seems to be a promising and stable marker for

epileptic and physiological brain tissue. Data suggest that the observed background activity either continuously oscillating or rather flat in nature is specific for a certain brain area in individual patients independent of sleep stage or day of recording.

As hypothesized, HFO occurring out of a non-oscillatory baseline are strongly linked to the SOZ, while a continuously oscillating background suggests unspecific and maybe physiological high frequency activity. This confirms findings of former studies with regard to pattern characteristics and possible epileptogenicity (Mari *et al.*, 2012; Melani *et al.*, 2013; Kerber *et al.*, 2014) in a large group of patients with a total of 143 280 10 s intervals with allocated patterns. Additionally, the flat background pattern with distinct HFO (pattern 2) is especially stable over the epileptic brain areas, while the continuously oscillating background pattern (pattern 1) shows more stability over distant brain regions. Estimation of pattern activity at one point in time is therefore promising to identify epileptic and non-epileptic brain regions.

Methodological considerations

The main purpose in the present study was to evaluate the long-term stability of HFO patterns, as former studies did not analyse HFO patterns over several days and different sleep-wake-stages (Kerber *et al.*, 2014). Therefore, we selected three day- and night-time EEG-segments per patient. We analysed interictal segments of 2 min each, assuming that less than 5 min of EEG-segments provide the same information as 10-min segments (Zelmann *et al.*, 2009). The 10-s interval for pattern allocation, however, was randomly chosen. We therefore cannot tell if smaller or larger time-intervals would have had an impact on pattern allocation.

In order to analyse HFO pattern stability, we decided to compute an entropy value for EEG segments, which measures the variability of the pattern. The stability of patterns in general and the influence of various parameters such as brain regions, SOZ/non-SOZ, recording techniques and time could be assessed in the present study. However, the chosen value presents methodical limitations: First of all, it gives no information about the sequence of pattern changes within an EEG segment. Secondly, the investigation does not show how different patterns relate in subsequent episodes of 10 s. Despite these limitations, entropy is a reliable measurement for the amount of change in patterns occurring within one brain region and allows statistical comparison of the stability of the EEG signal between different areas.

All of the 23 patients included in our study received stereotactic electrode implantation. Six patients received an implantation of additional subdural electrodes. Depth electrodes are mostly indicated when EEG recording is needed from buried grey matter (Zumsteg and Wieser, 2000) and deep brain structures have to be sampled (Spencer, 1989).

However, after implantation, a large number of stereotactic EEG electrode-contacts are not attached to the cortical surface (Iida and Otsubo, 2017). These contacts, which are hence located in white matter, are represented by pattern 0 in the present study. As expected, due to the large number of patients in our study implanted with stereotactic EEG, these contacts resulted in a dominance of pattern 0 in our analysis. To avoid the influence of these contacts on our statistical results, we excluded channels presenting exclusively pattern 0 from our analysis of pattern-probability and pattern entropy.

Distribution of patterns

Former studies on HFO patterns were limited to specific brain regions such as mesiotemporal structures and the occipital lobe, or to a specific type of electrode (Mari *et al.*, 2012; Melani *et al.*, 2013). Kerber *et al.* (2014) restricted their analysis to data that derived almost exclusively from patients with focal cortical dysplasia as the underlying pathology. In the present study, no such selection criteria were employed. A total of 2089 channels and 143 280 10 s intervals with allocated patterns from 23 patients were included. Like in previous studies, HFO occurring in a flat background EEG were linked to SOZ areas and most likely represent epileptic HFO. This observation was independent of the type of epilepsy, underlying pathology, brain region and electrode type. In contrast to pattern 2, pattern 1 showed a random distribution between SOZ and non-SOZ channels. This finding is consistent with studies on distinct HFO as pattern 2 is closest to of an distinct HFO.

Interestingly, both pattern types were significantly more frequent over the mesiotemporal than neocortical regions and this was true even after excluding pattern 0 channels occurring over white matter. Thus suggesting that the mesiotemporal structures are very active in generating physiological and epileptic HFO, as has been suggested before (Jacobs *et al.*, 2008, 2012, 2016). Additionally, brain regions of course are often not exclusively epileptic or physiologic in function and areas might generate physiological and epileptic HFO. Data on ripples in the mesiotemporal structures definitely suggest that epileptic and physiologic HFO occur within the same hippocampus (Jacobs *et al.*, 2016). This might be the reason why in some areas it was hard to identify one specific pattern resulting in a higher entropy.

The SOZ as the clinical gold standard for defining epileptic regions is of special interest with regard to pattern stability and HFO differentiation criteria. Mistaking physiological HFO for pathological could end up in surgically removing physiologically active brain regions that do not represent epileptic tissue (Jacobs *et al.*, 2016).

Despite many studies focusing on the differentiation between physiologic and pathologic HFO, no clear differentiation criteria was found up to the present (Nagasawa *et al.*, 2012; Wang *et al.*, 2013; Alkawadri *et al.*, 2014;

Kerber *et al.*, 2014). Lately, in a study of 123 patients, deviation of HFO measures from the nonepileptic mean at the whole-brain level was determined, taking into account the region-dependent phase-amplitude coupling between nonepileptic HFO and slow-wave (Motoi *et al.*, 2019). They found that their HFO phase-amplitude coupling measure rated by z-score improved the prediction of post-operative seizure outcome. Our results suggesting that HFO pattern 2 may help in differentiation between epileptic and physiologically active brain regions. We did not investigate pattern correlation with postoperative seizure outcome. Further studies are needed to compare the reliability and the predictive power of both methods.

Though, for further improvement and even more specific SOZ detection, a combination of different approaches of HFO-assessment, for example HFO pattern and interaction between HFO and slow waves of sleep or different sleep stages, should be investigated in larger studies.

In addition, it is well known that interictal epileptiform discharges as well as HFO are increased during slow wave sleep compared to wakefulness (Clemens *et al.*, 2003; Frauscher *et al.*, 2016). The HFO pattern from flat background, which is closely linked to the SOZ in the present study, was also significantly more prominent during slow wave sleep, which further supports the idea that this pattern is epileptic. On the contrary, no such changes were seen for HFO from oscillatory background, reflecting that these might be physiological and therefore occur during daytime.

Pattern-probability

Many studies investigating HFO and their ability to localize the SOZ, have focused on measuring the incidence inside and outside the SOZ by computing HFO-rates (Urrestarazu *et al.*, 2007; Andrade-Valença *et al.*, 2012; Dümpelmann *et al.*, 2015). Promising results were found with significantly higher HFO-rates inside than outside the SOZ (Cho *et al.*, 2012; Malinowska *et al.*, 2015; Pail *et al.*, 2017). Furthermore, it could be shown that SOZ detection on the basis of HFO-rates appears to be more specific and sensitive than SOZ detection using spikes, a well-established traditional marker (Jacobs *et al.*, 2008). The pattern analysis in the current study is independent of the actual HFO-rate. This might be an advantage for the clinical use for two reasons. First, a judgement of a pattern can be done from looking at very few screens of EEG. Our results suggest that the pattern remains stable and therefore longer analysis over several days is not necessary. Second, it has been complicated in clinical studies on HFO rates to define a threshold above which HFO occurrence is clinically relevant (Ochi *et al.* 2007; Jacobs *et al.*, 2018). The pattern analysis is independent of this threshold and rather relies on the high-frequency background activity, thus facilitating a clinical decision. The receiver operating characteristic curve analysis in our study presented a good performance of HFO occurring in quiet background to differentiate between SOZ and non-SOZ-channels. In the present study 2089 channels and 143 280 10 seconds intervals with allocated patterns from 23 patients were included. This is, so far, the largest investigated dataset with regard to analysis of HFO pattern and the SOZ. However, further studies investigating HFO pattern are needed to validate the results of this study.

Pattern entropy

Previous studies on HFO patterns did not focus on their long-term stability (Melani *et al.*, 2013; Kerber *et al.*, 2014). It is intriguing to suggest that identification of a typical pattern of a channel within the first minute of EEG can predict which brain areas are parts of the SOZ. Especially for clinical use and identification of epileptogenic areas, information about HFO pattern stability is essential. It is important to know the duration of EEG that needs to be analysed to gain valid information about HFO pattern. This might reduce the work load for epileptologists and reduce intracranial implantation of electrodes to a minimum of time. Our results indicate that HFO patterns in general appear to be a stable phenomenon. This stability was found to be independent of the used electrodes, brain structures and the sleep-wake cycle. Our results revealed lower entropy values inside than outside the SOZ suggesting that patterns generally remain more stable in time inside the SOZ. Moreover, our results indicate that especially HFO from non-oscillating background, the pattern which is considered most important in indicating the SOZ, appears to be more stable inside than outside the SOZ. From a functional point, it seems logical that the pathological epileptic pattern might be more fixed and stable than physiological activity which might be varying depending on the actual cognitive demand (Axmacher *et al.*, 2008; Frauscher *et al.*, 2018).

Despite this clinically relevant observation, the underlying mechanisms between the two different background patterns remain unclear.

Some studies suggest that physiologically occurring HFO display a longer and more continuous activity (Nagasawa *et al.*, 2012; Alkawadri *et al.*, 2014; Frauscher *et al.*, 2018). For the primary visual cortex, it has been shown that physiological HFO longer than 200 ms are generated spontaneously as well as upon a visual task (Nagasawa *et al.*, 2012; Nakai *et al.*, 2017) In our study, patterns 1 and 3 were both characterized by longer lasting oscillations and more internal variability. These might reflect physiologically active and oscillating brain regions and may be used as a stable fingerprint in identifying those areas. Nevertheless, no subdivision of neocortical channels has been undertaken in the present study. Thus, we can only suggest that the mentioned phenomenon of longer-lasting physiological oscillations in occipital channels and our patterns reflect the same phenomenon.

Further studies, investigating patterns 1 and 3 and their correlation with specific neocortical areas and tasks, are needed.

The epileptic pattern is characterized by sporadic short HFO out of a flat baseline. It is currently discussed that epileptic HFO derive from synchronous action potential firing of principal cells (Jiruska *et al.*, 2017). The flat baseline between oscillations might reflect effective inhibition between firing bursts. In contrast to the other patterns, this pattern is also defined by a more stereotypical cluster and less variability. This stereotypic cluster seems to represent stable brain activity inside the SOZ, mirroring the pathologically interconnected firing neurons in a pathological network which we consider responsible for epileptic HFO generation (Bragin *et al.*, 2000).

Conclusion

Visual or automatic analysis of individual HFO events is still considered to be the gold standard for HFO assessment (Frauscher *et al.*, 2017). Analysis of HFO rates is complicated by the inability to distinguish between physiological and pathological events. The present study proposes HFO patterns as a possible new and faster way of assessing HFO in clinical settings. In this analysis, high-frequency activity in the surrounding background EEG is more important than the single HFO event. HFO occurring in a flat non-oscillatory baseline are closely linked to the SOZ. Analysis of baseline activity might reliably be used to differentiate between physiological and pathological HFO. Moreover, interaction between HFO and background activity is not subject to alterations but represents stable phenomena. Therefore, HFO pattern analysis is reliable even after looking at only short time segment. Additionally, pattern stability suggests that different HFO-background patterns have distinct underlying brain mechanisms and could help identifying epileptic and physiologically active brain regions.

Supplementary material

Supplementary material is available at *Brain Communications* online.

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Competing interests

The authors report no competing interests.

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