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High-frequency oscillations in scalp EEG: A systematic review of methodological choices and clinical findings

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HIGHLIGHTS

- Scalp high-frequency oscillations (HFOs) were detected in most people with epilepsy, particularly in focal epilepsy and severe epilepsy types.
- Scalp HFOs were more specific than spikes in localizing the epileptogenic zone and predicting outcome.
- Methodologies were heterogeneous; future studies should use more homogeneous methods to improve comparability and applicability.

ABSTRACT

Objective: Pathological high-frequency oscillations (HFOs) in intracranial EEG are promising biomarkers of epileptogenic tissue, and their physiological counterparts play a role in sensorimotor and cognitive function. HFOs have also been found in scalp EEG, but an overview of all studies is lacking. In this systematic review, we assessed the methodology to detect scalp HFOs and their clinical potential.
Methods: We searched PubMed, Embase and the Cochrane Library for studies on HFOs in scalp EEG, and extracted methodological and clinical data.
Results: We included 60 studies with data from 1149 unique individuals. Two-thirds of studies analyzed HFOs visually in the time or time–frequency domain, and one-third automatically with visual validation. Most studies evaluated interictal ripples during sleep in children. Pathological HFOs were overall better than spikes in localizing the epileptogenic zone and predicting outcome, correlated negatively with cognition and positively with disease activity and severity, and decreased after medical and surgical treatment.
Conclusions: The methodologies of the 60 studies were heterogeneous, but pathological scalp HFOs were clinically valuable as biomarkers in various situations, particularly in children with epilepsy.
Significance: This systematic review gives an extensive overview of methodological and clinical data on scalp HFOs, establishing their clinical potential and discussing their limitations.

Abbreviations: 10-20 EEG, EEG according to the international 10-20 system; ACECTS, atypical childhood epilepsy with centrotemporal spikes; AUC, area under receiver operating characteristic curve; CECTS, childhood epilepsy with centrotemporal spikes; CSWS, epileptic encephalopathy with continuous spike-and-wave during sleep; EEG, electroencephalography; EZ, epileptogenic zone; FIR, finite impulse response; HD-EEG, high-density EEG; HFA, high-frequency activity; HFO, high-frequency oscillation; IIR, infinite impulse response; MEG, magnetoencephalography; NREM, non-rapid eye movement sleep; REM, rapid eye movement sleep; SWA, slow wave activity.

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1. Introduction

Scalp or surface electroencephalography (EEG) has been widely used for nearly a century by neurologists and neuroscientists to assess brain function. The 0.3–70 Hz band was studied traditionally, but higher frequencies have recently gained interest. High-frequency activity (HFA) is all brain activity above 80 Hz, and high-frequency oscillations (HFOs) are defined as discrete EEG events of at least four oscillations that clearly stand out from the background pattern (Jacobs et al., 2009b; Noorlag et al., 2019), and are subdivided into ripples (80–250 Hz) and fast ripples (250–500 Hz). HFOs can be pathological or physiological, and can be evoked or occur spontaneously (Thomschewski et al., 2019).

The first glimpses of evoked and spontaneous HFOs were seen as early as 1976 during median nerve stimulation (Cracco and Cracco, 1976) and 1992 during seizures in intracranial EEG recordings (Allen et al., 1992; Fisher et al., 1992). Later on, pathological and physiological HFOs were found in high-pass filtered EEG signals of intracranial microelectrodes (Bragin et al., 1999a, 1999b) and macroelectrodes of people with refractory epilepsy (Akiyama et al., 2005; Axmacher et al., 2008; Jirsch et al., 2006).

Physiological HFA and HFOs play a role in sensorimotor and cognitive function (Axmacher et al., 2008; Fukuda et al., 2008; Nakai et al., 2017; Norman et al., 2019; Vaz et al., 2019), and pathological or epileptic HFOs seem promising biomarkers of epileptogenic tissue in epilepsy surgery candidates (Thomschewski et al., 2019). It is challenging to distinguish pathological from physiological HFOs. HFOs that co-occur with spikes and those generated during seizures are likely pathological, and in contrast, HFOs evoked by sensorimotor and cognitive are likely physiological. Unfortunately, we are currently not able to distinguish them with certainty (Thomschewski et al., 2019). The stakes for pathological HFOs are high, because in epilepsy - one of the most prevalent neurological disorders (GBD 2015 Neurological Disorders Collaborator Group, 2017) −30 to 40% of patients continue to have seizures despite antiseizure medication (Kwan and Sander, 2004). Even after epilepsy surgery, which is the sole curative treatment for epilepsy, only 30–40% of patients are free of disabling seizures (Lamberink et al., 2020). Retrospective and prospective studies have investigated whether HFOs can localize the epileptogenic zone (EZ) more accurately than the seizure onset zone and irritative zone, which were traditionally used in combination with neuroimaging modalities in epilepsy surgery planning (van 't Klooster et al., 2015; Jacobs et al., 2018).

HFO research accelerated when pathological interictal HFOs were discovered non-invasively in scalp EEG (Kobayashi et al., 2010) and magnetoencephalography (MEG) (van Klink et al., 2016c). MEG is an expensive neurophysiologic modality and has a limited availability, even in large epilepsy surgery centers. Scalp EEG is widely available and easily repeatable, and thus HFO analysis in scalp EEG will benefit many people if it proves to be clinically valuable.

A systematic review of all studies on HFOs in scalp EEG is lacking. We aim to assess the methodology and clinical potential of HFOs in scalp EEG. We will give an overview of the current state-of-the-art and describe gaps of knowledge. We will discuss limitations of scalp HFOs and provide recommendations for future studies.

2. Methods

2.1. Search strategy

We conducted a systematic search in PubMed, Embase and the Cochrane Library (January 1, 2021), combining synonyms for scalp EEG and HFOs (Supplementary Table 1). We did not use any limits in our search. We included high-gamma frequencies because some studies refer to high-gamma frequencies as being up to 200 Hz. When studies did not subdivide EEG events into gamma frequencies, ripples, or fast ripples, we referred to these events as *fast oscillations* (all activity above 30–40 Hz merged, including activity in the HFO (>80 Hz) band). To clarify, we only included studies that thus also contained brain activity in the HFO band. This systematic review was performed in accordance with the PRISMA statement (Moher et al., 2009). The PRISMA statement is primarily intended for systematic reviews and meta-analyses of clinical intervention studies. This systematic review focused on clinical non-intervention studies, but we adhered to the guideline as closely as possible.

We removed duplicate records and conducted a step-by-step selection based on title, abstract and full-text (LN, supervised by MZ). Discrepancies were discussed in meetings and consensus was reached. We checked the completeness of our search by hand-searching the reference lists of inclusions, and running them through Scopus and Web of Science.

2.2. Selection criteria

We consecutively applied the following inclusion criteria: 1) research had to concern human subjects; 2) studies had to be written in English;3) studies had to be published, and concern original and full-text research (including observational studies); 4) (one of) the main aim(s) of the studies was to report brain activity above 80 Hz (*high-frequency activity* (HFA)) in scalp EEG, either in the time domain or the single event time–frequency domain. 5) Scalp EEG was recorded with a sample frequency of at least 300 Hz to be able to assess activity above 80 Hz.

Editorials, letters (without original research), study protocols, conference abstracts and narrative reviews were excluded. We also excluded studies on solely HFOs in MEG or intracranial EEG, and studies on solely gamma frequencies (<80 Hz). In addition, studies on solely HFA in the averaged time–frequency domain - but not in the single event time–frequency domain - were excluded. Finally, we decided to exclude studies that only reported evoked HFOs, because the assessment of evoked potentials - a large field of research - is not current clinical practice during scalp EEG recordings, and goes beyond the scope of this systematic review.

2.3. Quality assessment

We globally assessed the methodological quality of the included studies based on their study designs, and subsequently decided if a formal quality assessment with use of appropriate tools - such as the QUADAS-2 tool for diagnostic studies (Whiting et al., 2011), or the QUIPS tool for prognostic studies (Hayden et al., 2013) - could be performed and would be contributory.

2.4. Data extraction and presentation

Methodological results are presented in a descriptive manner. To assess the methodology, we extracted the HFO and epoch subtype, EEG recording conditions (montage, sample frequency and filters) and HFO analysis methods (visual detection in the time or time–frequency domain, or automatic detection with or without visual validation).

Clinical findings are presented in a pooled and descriptive manner. To assess the clinical potential of scalp HFOs, we extracted characteristics of study populations (age and epilepsy type) and HFO findings (frequency, duration, rate [HFOs/min] and co-occurrence with spikes and seizures). HFO findings in scalp EEG were pooled per epilepsy type. We created a table for the localizing

value of scalp HFOs in focal epilepsy (including sensitivity, specificity and accuracy, using various reference standards of the EZ), and a figure showing percentages of people with concordance between the location of scalp HFOs and various EZ reference standards. Finally, we created a table for the diagnostic and prognostic value of scalp HFOs with use of clinical outcome parameters, such as eventual epilepsy development, disease activity and severity.

3. Results

3.1. Selection

We included 53 studies after the step-by-step selection (Fig. 1). Hand-searching their reference lists and running them through Scopus and Web of Science resulted in seven extra inclusions, yielding in total 60 studies with data from 1149 unique individuals.

3.2. Quality assessment

The study populations, research questions and methods of the 60 studies were heterogeneous and could thus not be reliably compared. In addition, based on the study designs (mainly retrospective case-series and cohort studies), the methodological quality was considered low with an inherent high risk of bias. Therefore, we decided not to perform a formal quality assessment.

3.3. Methodological choices

Methodological details per study can be found in Supplementary Table 2.

The 60 studies can be grouped as follows: ripples only were analyzed by 40, fast ripples only by one, and fast oscillations (all activity above 30–40 Hz merged, including activity in the HFO (>80 Hz) band) by 14. To clarify, two of the 14 studies contained merged HFO band activity (that was not subdivided into ripples and fast ripples), and 12 merged gamma (30–80 or 40–80 Hz) and HFO band activity. Three studies reported ripples and fast ripples, one ripples and fast oscillations, and one ripples, fast ripples and fast oscillations.

Fifty-seven studies evaluated pathological or epileptic HFOs, two physiological HFOs and one both pathological and physiological HFOs. Forty-four of the 58 studies on pathological HFOs evaluated interictal epochs, ten ictal epochs, and four both ictal and interictal epochs. The median interictal epoch duration was 12 min, with a range from 10 s to 111 h. Studies on both interictal and ictal epochs reported that ictal epochs showed a higher HFO rate than interictal ones (Chaitanya et al., 2015; Kobayashi et al., 2017, 2015). Ictal HFOs preceded clinical symptoms (Inoue et al.,

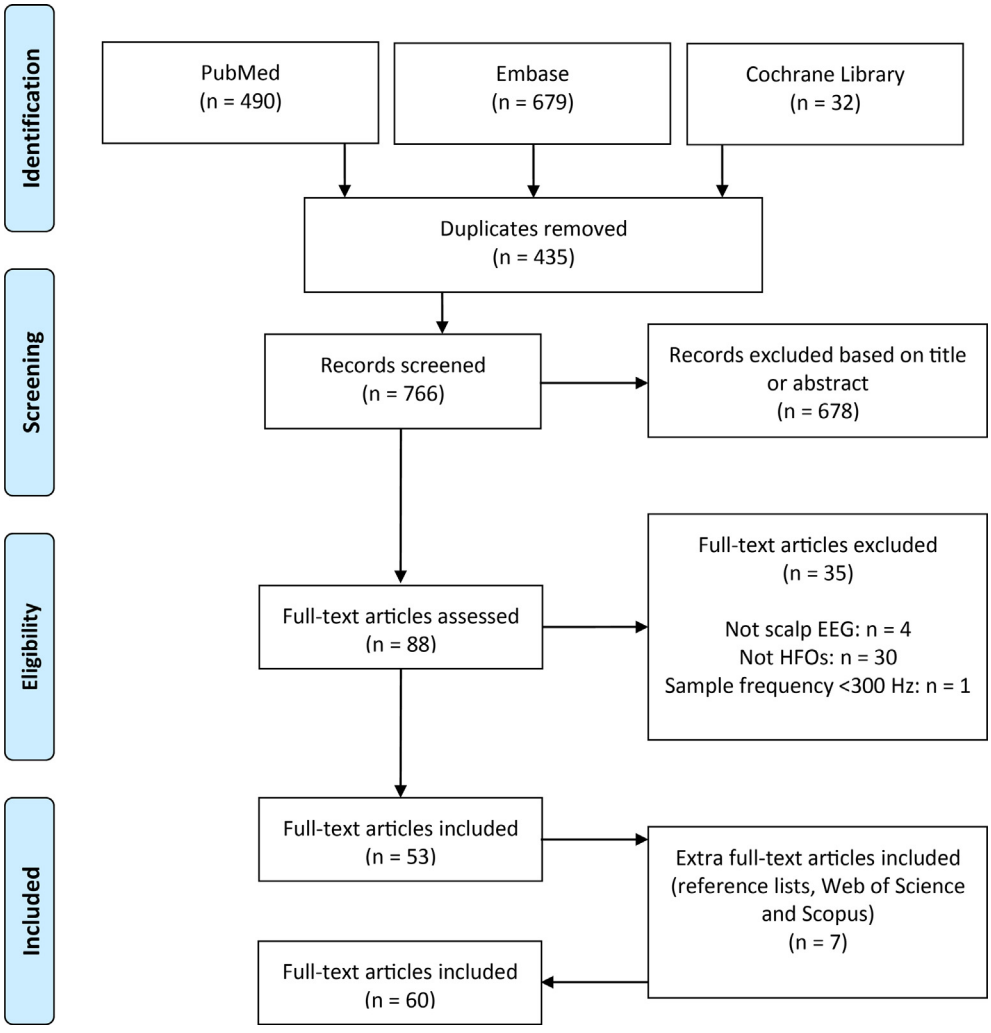

Fig. 1. Flowchart of the step-by-step selection. HFO = high-frequency oscillations (>80 Hz).

2008; Iwatani et al., 2012; Kobayashi et al., 2018, 2009, 2004; Murai et al., 2020; Nariai et al., 2017), and were suggested to indicate focal seizure onset despite generalized conventional EEG findings and bilateral clinical symptoms (Kobayashi et al., 2018; Nariai et al., 2017).

One of the 60 studies evaluated HFOs solely during wakefulness (during absence seizures, provoked by hyperventilation) (Ikemoto et al., 2020). Thirty-five studies assessed epochs during sleep and 11 epochs during both sleep and wakefulness. Another 12 studies did not report vigilance state. One study assessed people with an altered level of consciousness (Ferrari-Marinho et al., 2020). Of the 46 studies that assessed sleep, 35 assessed non-rapid eye movement sleep (NREM), none solely rapid eye movement sleep (REM), three NREM and REM, and eight did not report sleep stages. Pathological HFOs were more often detected during sleep than during wakefulness (van Klink et al., 2016a; Klotz et al., 2021; McCrimmon et al., 2021).

Seventeen studies analyzed HFOs visually in the time domain, two in the time–frequency domain and 18 in both domains. Nineteen studies automatically detected HFOs and validated them visually in the time domain (N = 13), the time–frequency domain (N = 2) or in both domains (N = 4). One study analyzed HFOs visually and automatically in the time domain, and two studies visually and automatically in both domains. In addition to visual detection in the time domain of interictal and ictal HFOs, Chaitanya et al. detected ictal ripples with use of independent component analysis with visual validation in the time domain and single event time–frequency domain (Chaitanya et al., 2015). When visual detection in the time domain was compared with the time–frequency domain, HFO analysis in the time–frequency domain showed more HFA than the time domain (Ikemoto et al., 2018; van Klink et al., 2016a; Kobayashi et al., 2011; Shibata et al., 2016), but this is not reflected in a stronger correlation with disease activity (van Klink et al., 2016a; Shibata et al., 2016). Intra- and interrater reliability of HFOs was favorable, with moderate to almost perfect kappas (0.55–0.92) (Cao et al., 2019; Chu et al., 2017; Kramer et al., 2019; Nariai et al., 2018) and percentages of agreement (63–83%) (Charupanit et al., 2018; McCrimmon et al., 2021). Three studies compared automatic detection with visual validation with automatic detection without visual validation (Kramer et al., 2019; McCrimmon et al., 2021; Nariai et al., 2020), and it is remarkable that one reported that 97% of participants (people with epilepsy and controls) showed ripples before visual validation, but only 33% after visual validation (mostly people with active epilepsy) (Kramer et al., 2019).

Most studies recorded EEG according to the international 10–20 system (10–20 EEG), and a median of 19 channels (range 4–216) was used for HFO analysis. When different electrode densities were compared, fewer HFOs were detected with 10–20 EEG compared with high-density EEG (HD-EEG), and HFOs in 10–20 EEG may have led to wrong localization of the presumed EZ (Avigdor et al., 2021; Kuhnke et al., 2018).

Thirty-one studies used a bipolar montage, 11 a referential montage (ten to A1 and A2, one not specified), nine an average montage, and one a Laplacian montage. One study did not report montage, and seven studies used more than one montage: four studies used both a bipolar and average montage, two a bipolar and referential montage, and one a bipolar and Laplacian montage.

Twenty-four studies recorded EEG at 500–600 Hz, 12 at 1000–1600 Hz and 17 at 2000 Hz or more. Seven studies reported more than one sample frequency, and three used a sample frequency of less than 500 Hz for some of their EEG recordings (Besio et al., 2014; Nariai et al., 2017; Toole et al., 2019).

High-pass filters, which were reported by 59 studies, ranged from 30 to 250 Hz, and 46 studies reported low-pass filters (range 100–1300 Hz). Finite impulse response (FIR) filters were most often used for HFO analysis (26 studies), and two studies used infinite impulse response (IIR) filters (McCrimmon et al., 2021; Toole et al., 2019). Others reported only hardware filters or did not report filter type.

New technologies were described in some studies. Two studies recorded EEG with tripolar concentric ring electrodes (Besio et al., 2014; Toole et al., 2019), and found that these electrodes were more sensitive to record fast oscillations than conventional ones (Besio et al., 2014). Pizzo et al. used subdermal electrodes and were the first to record fast ripples in scalp EEG (Pizzo et al., 2016b). Three studies recorded scalp and intracranial EEG simultaneously (Kuhnke et al., 2019; Pizzo et al., 2016b; Zelmann et al., 2014), and found that scalp ripples were generated by small cortical sources (Zelmann et al., 2014). MEG was recorded simultaneously with EEG in four studies (Dirodi et al., 2019; van Klink et al., 2019; Papadelis et al., 2016; Tamilia et al., 2020), and although MEG showed fewer ripples than EEG (Dirodi et al., 2019; Tamilia et al., 2020), these ripples might be more sensitive and specific for the presumed EZ (van Klink et al., 2019). Van Klink et al. applied beamforming to HD-EEG (van Klink et al., 2019, 2018), and detected more ripples in virtual electrodes than in physical ones, which improved localization of the presumed EZ (van Klink et al., 2018). Source imaging or localization was used by six studies (Avigdor et al., 2021; Dirodi et al., 2019; Lu et al., 2014; Papadelis et al., 2016; Tamilia et al., 2020; Toole et al., 2019), and ictal direct current shifts (infraslow activity) and HFOs were simultaneously recorded by another (Murai et al., 2020). Finally, HFO coupling with slow wave activity (SWA) gained interest, and was evaluated in children with epileptic spasms in ictal (Kobayashi et al., 2016) and interictal epochs (Bernardo et al., 2020; Nariai et al., 2020).

3.4. Clinical findings

Clinical details and main findings per study can be found in Supplementary Table 3.

Children were included in 37 studies (829 patients), adults in 12 (172 patients) and both children and adults in nine studies (127 patients) (and two studies did not report age [21 patients]). It has been hypothesized that children show more HFOs than adults, but findings in this systematic review were contradictory (Klotz et al., 2021; Kobayashi et al., 2009; Ohuchi et al., 2019; Tsuchiya et al., 2020).

Table 1 shows an overview of HFO findings in scalp EEG, pooled per epilepsy type. The most extensively studied epilepsy types are focal epilepsy (24 studies; 335 patients), childhood epilepsy with centrotemporal spikes (CECTS) (7 studies; 191 patients) and epileptic spasms (10 studies; 150 patients). Detectability (the percentage of patients that shows HFOs) is high in focal epilepsy and severe epilepsy types, such as atypical childhood epilepsy with centrotemporal spikes (ACECTS) and epileptic encephalopathies. Fast ripples were detected in 83% of people with focal epilepsy (3 studies; 24 patients), and in 0% of controls (1 study; 4 patients). Of note, five studies analyzed fast ripples (Bernardo et al., 2020, 2018; Charupanit et al., 2018; Nariai et al., 2018; Pizzo et al., 2016b). HFO rates were calculated in seven different manners, which cannot be reliably compared, and showed wide ranges, even within epilepsy types (for example, focal epilepsy 0.02–145.00/min). In general, HFO rates were lower in controls compared to people with epilepsy. Most HFOs co-occurred with spikes (51–98%), while the minority of spikes co-occurred with HFOs (14–53%). The number of HFOs correlated with the number of spikes (Fahoum et al., 2014; Kuhnke et al., 2018; Melani et al., 2013), but HFOs propagated less than spikes (Avigdor et al., 2021; Cuello-Oderiz et al., 2017; Gong et al., 2018; van Klink et al., 2016b; Kramer et al., 2019; Tamilia et al., 2020; Zelmann et al., 2014). When HFOs and spikes co-occurred, the onset of most HFOs

Table 1
Overview of high frequency oscillation (HFO) findings in scalp EEG, pooled per epilepsy type. Which studies were pooled per epilepsy type and how rate was calculated can be found in the footnotes. Some studies described more than one epilepsy type and are thus listed more than once. When multiple options per HFO finding per study were available, we preferred active epilepsy (before treatment rather than after treatment), EEG according to the international 10–20 system rather than high-density EEG, physical electrodes rather than virtual electrodes (created by beamforming), visual HFO detection (and validation) rather than (only) automatic HFO detection, and analysis in the time domain rather than analysis in the time–frequency domain. We found these options to be closest to the gold standard (visual detection) and to contribute most to applicability. We do not report findings of solely gamma frequencies (<80 Hz). Eleven studies were not categorized: four studies did not contain unique patients (von Ellenrieder et al., 2016, 2012; Kobayashi et al., 2016; Mooij et al., 2018), study populations were heterogeneous in four studies (153 patients) (Klotz et al., 2021; Mooij et al., 2017; Nariai et al., 2018; Ohuchi et al., 2019), one study concerned Rolandic spikes (22 patients) (van Klink et al., 2016a), one 15 patients with altered consciousness (Ferrari-Marinho et al., 2020) and one study reported HFO findings in 58 EEG recordings (≥1 EEG recording per patient) (Cuello-Oderiz et al., 2017).

			Focal epilepsy types				Generalized epilepsy types			Epileptic encephalopathies			Controls[2]
			Focal epilepsy[1]	CECTS	ACECTS	PS	IGE	AE	ME	ES	CSWS	LGS	
N (studies)			24[a]	7[b]	2[c]	2[d]	1[e]	2[f]	1[g]	10[h]	4[i]	1[j]	5[k]
N (patients)			335	191	21	42	7	55	21	150	56	20	58
Detectability[3] (%) (# studies; patients)	**R**	**II**	79.6 (17;260)	38.3 (6;175)	71.4 (1;14)	42.9 (2;42)	42.9 (1;7)			88.9 (1;9)	83.9 (4;56)		58.1 (2;31)
		I	100 (1;1)						47.6 (1;21)	81.8 (2;11)			
	FR	**II**	83.3 (3;24)										0 (1;4)
	FO[4]	**II**	81.8 (4;44)							95.6 (2;45)			66.7 (1;6)
		I								100 (4;63)		65.0 (1;20)	
Frequency range (Hz) (# studies; patients)	**R**	**II**		94–235 (4;95)	115–153 (1;7)	94–152 (2;42)					86–250 (3;35)		
		I	80–110 (1;1)					86–135 (2/55)					
	FR	**II**	265–337 (2;17)										
	FO[4]	**II**	45–425 (3;44)							41–141 (1;17)			41–49 (1;17)
		I							41–123 (1;21)	41–145 (4;46)		43–102 (1;20)	
Duration range (ms) (# studies; patients)	**R**	**II**	31–70 (2;38)										
	FR	**II**	11–36 (3;24)										
	FO[4]	**II**	35–104 (1;23)										
		I								200–1100 (2;26)			
Rate[5] range of study means or medians (/min) (# studies; patients)	**R**	**II**	0.12–1.57[q] (8;122) 0.21–1.43[o] (4;67) 1.00[l] (1;6) 118.00[n] (1;23)	1.86–4.49[n] (2;32) 3.78[q] (1;10) 7.50[m] (1;10)	30.19–85.79[n] (2;21)		0.56[q] (1;7)			2.30[r] (1;7)	43.20[r] (1;21)		0.27[m] (1;13) 0.98[o] (1;18)
	FR	**II**	0.09–0.29[q] (2;17) 0.74[r] (1;7)							1.95[r] (1;7)			
	FO[3]	**II**	145.00[n] (1;23) 0.02[m] (1;18)							2.41[p] (1;23) 66.00[n] (1;17)			1.00[n] (1;17) 0.01[m] (1;6)
		I								116.20[n] (1;17)			
% HFOs with spikes (# studies; patients)	**R**	**II**	51.4 (7;141)		56.9 (1;14)		93.0 (1;7)				93.0 (2;24)		
	FR	**II**	61.5 (1;7)										
	FO[4]	**II**	97.7 (1;23)							93.2 (1;17)			
% spikes with HFOs (# studies; patients)	**R**	**II**	13.5 (7;150)	17.5 (2;28)	23.4 (2;21)			52.7 (1;9)			35.3 (1;3)		

Table 1 (*continued*)

			Focal epilepsy types				Generalized epilepsy types			Epileptic encephalopathies			Controls[2]
			Focal epilepsy[1]	CECTS	ACECTS	PS	IGE	AE	ME	ES	CSWS	LGS	
% seizures with HFOs (# studies; patients)	**R**	**I**	31.3 (1;1)					71.7 (1;9)		65.5 (2;16)			
	FO[4]	**I**							88.4 (1;21)	82.1 (2;26)		46.3 (1;20)	

ACECTS = atypical childhood epilepsy with centrotemporal spikes, AE = absence epilepsy, CECTS = childhood epilepsy with centrotemporal spikes, CSWS = epileptic encephalopathy with continuous spike-and-wave during sleep, ES = epileptic spasms, FO = fast oscillation (>30–40 Hz), FR = fast ripple (250–500 Hz), IGE = idiopathic generalized epilepsy (not further specified), HFO = high-frequency oscillation (>80 Hz), I = ictal, II = interictal, LGS = Lennox-Gastaut syndrome, ME = myoclonic epilepsy, PS = Panayiotopoulos syndrome, R = ripple (80–250 Hz).

[1] Mostly refractory.
[2] Data concerns 52 children and six adults.
[3] Percentage of patients that shows HFOs.
[4] All activity above 30–40 Hz merged, including activity in the HFO (>80 Hz) band that was not subdivided into ripples and fast ripples.
[5] Studies have used different manners to calculate rate. We indicate with letters which method each study used (see below for letters' legend). Of note, rates can only be reliably compared when the HFO analysis method and the manner to calculate rate are the same.

[a] (Andrade-Valenca et al., 2011; Avigdor et al., 2021; Bernardo et al., 2018; Besio et al., 2014; Boran et al., 2019; Charupanit et al., 2018; Dirodi et al., 2019; Fahoum et al., 2014; Gerner et al., 2020; van Klink et al., 2019, 2018, 2016b; Kuhnke et al., 2018, 2019; Lu et al., 2014; Melani et al., 2013; Murai et al., 2020; Papadelis et al., 2016; Pizzo et al., 2016b, 2016a; Tamilia et al., 2020; Toole et al., 2019; Tsuchiya et al., 2020; Zelmann et al., 2014).
[b] (Chu et al., 2017; Ikemoto et al., 2018; Kobayashi et al., 2011; Kramer et al., 2019; Qian et al., 2016; Shibata et al., 2016; Zhang et al., 2020).
[c] (Ikemoto et al., 2018; Qian et al., 2016).
[d] (Kobayashi et al., 2011; Shibata et al., 2016).
[e] (Pizzo et al., 2016a).
[f] (Chaitanya et al., 2015; Ikemoto et al., 2020).
[g] (Kobayashi et al., 2018).
[h] (Bernardo et al., 2020; Inoue et al., 2008; Iwatani et al., 2012; Kobayashi et al., 2017, 2015, 2013, 2004; McCrimmon et al., 2021; Nariai et al., 2020, 2017).
[i] (Cao et al., 2019; Gong et al., 2018; Kobayashi et al., 2010; Toda et al., 2013).
[j] (Kobayashi et al., 2009).
[k] (Bernardo et al., 2018; Gerner et al., 2020; Kobayashi et al., 2015; Kramer et al., 2019; McCrimmon et al., 2021).
[l] All patients, HFO times.
[m] All patients, per channel (all channels).
[n] All patients, across channels.
[o] Only patients with HFOs, HFO times.
[p] Only patients with HFOs, per channel (all channels).
[q] Only patients with HFOs, per channel (only channels with HFOs).
[r] Only patients with HFOs, across channels.

preceded the onset of spikes (Avigdor et al., 2021; van Klink et al., 2016b). The co-occurrence of seizures and HFOs was variable and might depend on seizure type (from 31.3% for focal seizures [one patient], to 88.4% for myoclonic seizures [21 patients]).

Almost all studies evaluated people with epilepsy, but Ferrari-Marinho et al. analyzed gamma oscillations and ripples in patients with altered consciousness (Ferrari-Marinho et al., 2020), and reported that a high rate of fast oscillations might indicate the presence of a structural brain lesion. It was reported that superficial lesions show more ripples than deep ones, and that HFO occurrence is thus influenced by lesion depth (Avigdor et al., 2021; Cuello-Oderiz et al., 2017). Lesion type, however, did not affect HFO occurrence (Cuello-Oderiz et al., 2017).

Mooij et al. detected physiological ripples in children without spikes (17 children without epilepsy, six with epilepsy) (Mooij et al., 2017). These ripples were mostly seen in central and midline channels, co-occur with sleep-specific transients in 74%, and have highest rates during light sleep (Mooij et al., 2018).

3.4.1. Localizing value of scalp HFOs

Six studies (Andrade-Valenca et al., 2011; von Ellenrieder et al., 2016; van Klink et al., 2019, 2018; Melani et al., 2013; Tamilia et al., 2020) reported the value of scalp HFOs for localizing the presumed EZ. Reference standards for the EZ ranged from scalp seizure onset zone to intracranial ripples (Table 2). Overall, scalp HFOs were less sensitive for localizing the presumed EZ than spikes and gamma frequencies, but more specific and accurate.

In Fig. 2, percentages of people with concordance between the location of scalp HFOs and EZ reference standards are plotted for focal epilepsy (**A**; 11 studies, 119 patients) and West syndrome (**B**; 4 studies, 21 patients [with structural brain lesions or focal seizures]). EZ reference standards were heterogeneous and ranged from epileptogenic hemisphere to resection area. Overall, the location of scalp HFOs was moderately concordant with the presumed EZ in both focal epilepsy and West syndrome, and concordance increased when EEGs were recorded with higher electrode densities. In studies with relatively low concordance, this could partially be due to other factors, such as the use of few electrodes (Pizzo et al., 2016b) or the underlying pathology (for example, unilateral reduced brain volume (Kobayashi et al., 2017)). Studies that evaluated concordance between scalp HFOs and EZ reference standards another level than patient-level (for example, channel- or HFO-level) are not plotted in Fig. 2, but similar percentages were found (78–100%; (Bernardo et al., 2018; Besio et al., 2014; Dirodi et al., 2019; Murai et al., 2020; Tamilia et al., 2020)). More details can be found in Supplementary Tables 4 and 5.

3.4.2. Diagnostic and prognostic value of scalp HFOs

Six studies (Boran et al., 2019; van Klink et al., 2016a; Klotz et al., 2021; Kramer et al., 2019; Nariai et al., 2020; Tamilia et al., 2020) evaluated the value of scalp HFOs for a range of clinical outcome parameters, such as eventual epilepsy development, disease activity and severity (Table 3). HFOs were in general less sensitive for outcome prediction than spikes, but more specific and had a larger area under receiver operating characteristic curve (AUC). The predictive value further improved when a low-noise amplifier was used (Boran et al., 2019), but not when HFO coupling with 0.5–1 or 3–4 Hz SWA was added (Nariai et al., 2020). Remarkably, Klotz

Table 2
Localizing value of scalp high-frequency oscillations (HFOs). All studies assessed interictal epochs. Sensitivity, specificity and accuracy are presented as percentages.

Study	N	# channels	EZ reference standard	Concordance level[1]	Analysis level	Event	Sens.	Spec.	Acc.	AUC
(Andrade-Valenca et al., 2011)	15	31	Scalp SOZ	NA	Channel	S	100	30	43	
						G	82	68	70	
						R	48	89	81	
(Melani et al., 2013)	32	31	Scalp SOZ	NA	Channel	S	78	50	54	
						G	66	76	74	
						R	48	83	70	
(von Ellenrieder et al., 2016)[2]	17	31	ROI[3]	Lobar	Patient	G	82			
						R	65			
(van Klink et al., 2018)	9	PE: 53 or 74 VE: 79	ROI[3]	NA	Channel	R	VE: 55	VE: 73		PE: 0.56 VE: 0.65
(van Klink et al., 2019)	30	PE: 60[4] VE: 2367	ROI[3]	At least partial	Patient	R (threshold: 8)	VE: 80	VE: 83		
(Tamilia et al., 2020)	17	72[4]	Intracranial R	Within 5 mm	Scalp R sources[5]	R	32			

Acc. = accuracy, AUC = area under receiver operating characteristic curve, EZ = epileptogenic zone, G = gamma (30–80 or 40–80 Hz), HFO = high-frequency oscillation (>80 Hz), NA = not applicable, PE = physical electrodes, R = ripple (80–250 Hz), ROI = region of interest, S = spike, Sens. = sensitivity, Spec. = specificity, SOZ = seizure onset zone, VE = virtual electrodes (created by beamforming), VV = visual validation.
[1] For example, hemispheral/lobar/sublobar, or partial/full.
[2] The same patients were also included in Andrade-Valenca 2011 and Melani 2013.
[3] Based on available clinical data (for example, resection area, intracranial and/or scalp EEG and MRI).
[4] The number of used channels was not available, so we reported the number of recorded electrodes.
[5] Defined by source imaging.

et al. found that ripples-not-on-spikes were more predictive of experiencing a second seizure and eventual epilepsy development than ripples-on-spikes in children with a first seizure (Klotz et al., 2021). Others focused on ripples-on-spikes, with high diagnostic and prognostic values in children with CECTS (van Klink et al., 2016a; Kramer et al., 2019) and focal epilepsy (Tamilia et al., 2020). In the latter study, removing generators of ripples-on-spikes, but not ripples-not-on-spikes, predicted good outcome after epilepsy surgery. Dirodi et al. also reported that most ripples-not-on-spikes are generated outside the presumed EZ, while the majority of ripples-on-spikes is generated inside (Dirodi et al., 2019).

Other studies evaluated correlations of scalp HFOs with disease activity and severity. Time since last seizure was shorter in children with CECTS and Panayiotopoulos syndrome when they showed HFOs (Kobayashi et al., 2011; Kramer et al., 2019), and the number of HFOs was positively correlated with the number of seizures in children with Rolandic spikes (van Klink et al., 2016a) and focal epilepsy (Boran et al., 2019), but not (consistently) in CECTS and Panayiotopoulos syndrome (Shibata et al., 2016). Detectability and HFO rates were high during status epilepticus and in severe epilepsy types, such as ACECTS and epileptic encephalopathies (Ikemoto et al., 2020; Nariai et al., 2020; Ohuchi et al., 2019; Qian et al., 2016; Tsuchiya et al., 2020). This was contradicted by Ikemoto et al. for early-stage ACECTS, but they reported that bilaterally synchronous HFA might distinguish early-onset ACECTS from CECTS (Ikemoto et al., 2018). Gerner et al. reported that HFO rates were not statistically significantly different between people with focal epilepsy and controls (Gerner et al., 2020), but this was contradicted by others for focal epilepsy and other epilepsy types (Bernardo et al., 2018; Kobayashi et al., 2015; Kramer et al., 2019; McCrimmon et al., 2021).

Cognition and its correlation with HFOs has been reported by two studies (Cao et al., 2019; Zhang et al., 2020). When HFOs persisted after treatment in children with epileptic encephalopathy with continuous spike-and-wave during sleep (CSWS), this was correlated with seizure recurrence and worse cognitive outcome, while this was not the case for spike-wave index $\geq$ 85% (Cao et al., 2019). In CECTS patients, those with HFOs performed worse on 82% of cognitive tasks and in 89% of cognitive domains than those without HFOs (Zhang et al., 2020).

HFOs decreased after treatment for West syndrome (Kobayashi et al., 2015), particularly HFOs that occurred during sleep (McCrimmon et al., 2021). HFOs were more sensitive to treatment than spikes in ACECTS (95 vs. 42% reduction (Qian et al., 2016)) and CSWS (91 vs. 40% reduction (Gong et al., 2018)), but the decrease of both HFOs and spikes was less pronounced in CSWS patients with a structural etiology compared to those with a genetic or unknown etiology (Gong et al., 2018). With regard to prediction of treatment response, Bernardo et al. reported similar HFO rates before treatment between responders and non-responders with epileptic spasms, but the preferred angle of HFO coupling with 2–3 Hz SWA differed between both groups (Bernardo et al., 2020).

Surgical treatment also reduced HFO rate (Boran et al., 2019). Patients with poor outcome after epilepsy surgery often showed widespread HFOs preoperatively (Kuhnke et al., 2019), and had a smaller percentage of HFOs resected compared to patients with good postoperative outcome (Kuhnke et al., 2019; Tamilia et al., 2020).

4. Discussion

We assessed the methodology and clinical potential of HFOs in scalp EEG, and included 60 studies with data from 1149 unique individuals.

Most studies evaluated 1) pathological HFOs, particularly ripples, 2) interictal epochs, 3) epochs during sleep, and 4) people with epilepsy, particularly children. Two-thirds of studies analyzed HFOs visually in the time or time–frequency domain, and one-third automatically, mostly with visual validation. EEG recording conditions, however, were heterogeneous (electrode density, montage, sample frequency, high- and low-pass filters). Detectability of HFOs in people with epilepsy was high (range 38.3–100%), particularly in focal epilepsy and severe epilepsy types, and most HFOs co-occurred with spikes. Pathological HFOs seemed to exceed

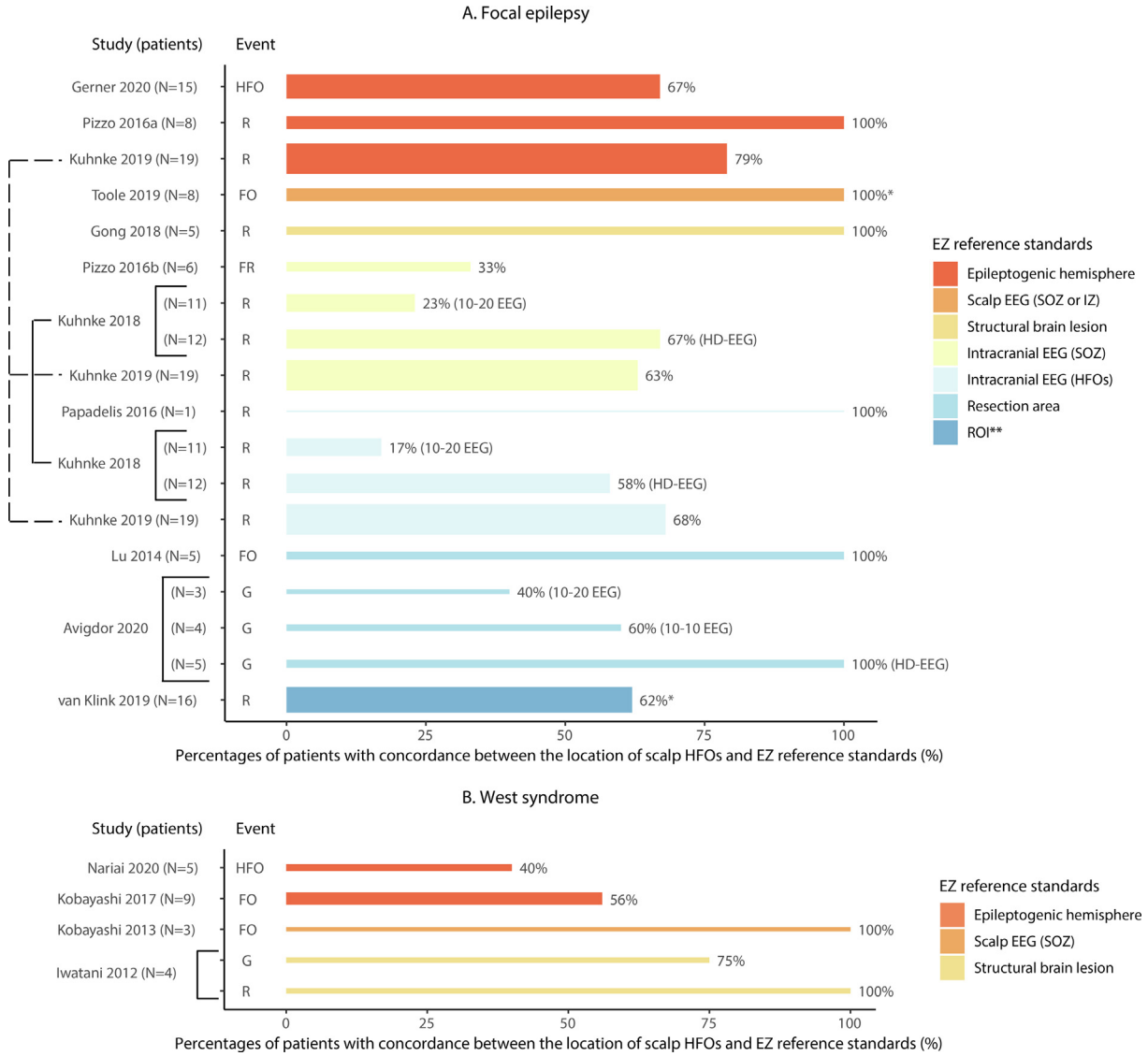

Fig. 2. Percentages of people with focal epilepsy (A; 11 studies, 119 patients) and West syndrome (B; 4 studies, 21 patients [with structural brain lesions or focal seizures]) with concordance between the location of scalp high-frequency oscillations (HFOs) and reference standards of the epileptogenic zone (EZ). The width of the bars is proportional to the number of patients. Only studies with patient-level analysis are shown. Studies with channel- or HFO-level analysis are listed in Supplementary Table 4 (Andrade-Valenca et al., 2011; Bernardo et al., 2020; Besio et al., 2014; Dirodi et al., 2019; Murai et al., 2020; Tamilia et al., 2020). More details of plotted studies can also be found in Supplementary Table 4 and 5. * Both partial and full concordance. ** Based on available clinical data (for example, resection area, intracranial and/or scalp EEG and MRI). EZ = epileptogenic zone, FO = fast oscillation (>30–40 Hz), FR = fast ripple (250–500 Hz), G = gamma (30–80 or 40–80 Hz), HFO = high-frequency oscillation (>80 Hz), R = ripple (80–250 Hz), SOZ = seizure onset zone.

spikes in their ability to localize the presumed EZ and predict clinical outcome. They were also shown to correlate with disease activity, severity and cognition, and responded to medical and surgical treatment.

4.1. Scalp HFOs in perspective

In the early years of HFO research, it was considered impossible to detect HFOs in scalp EEG, because their generators would be too small. Since then, the contrary has been proven by simulation studies (von Ellenrieder et al., 2014) and studies with simultaneous scalp and intracranial EEG (Zelmann et al., 2014), and the discovery of non-invasive HFOs accelerated HFO research. It was previously noted that the term HFOs is used for different phenomena and that definitions were lacking, after which terminology was proposed based on duration and visibility in the time and time–frequency domain to improve comparability and applicability (Noorlag et al., 2019). The presence of at least four oscillations - which has long been used to define HFOs (Jacobs et al., 2009b) - is not mentioned by one third of studies in this systematic review. When HFA subtypes are compared, HFA in the time domain (HFOs) seems to be more clinically valuable than HFA in the time–frequency domain. In intracranial EEG, HFOs helped to localize the seizure-onset zone, while HFA failed to do so (Jacobs et al., 2016). In scalp EEG, the number of ripples was positively correlated with the number of seizures, while the number of channels with HFA was not (van Klink et al., 2016a). Intracranial language task-related HFA in the time–frequency domain, however, predicts neuropsychological outcome after epilepsy surgery (Sonoda et al., 2021). The time–frequency domain requires data processing, which may be more challenging for clinicians than HFO analysis in the time domain.

In scalp EEG, findings are contradictory when it comes to the clinical value of ripples-on-spikes (better according to (Tamilia et al., 2020) and (Dirodi et al., 2019)) vs. ripples-not-on-spikes (better according to (Klotz et al., 2021)). This could partially be due to different study populations: Klotz et al. studied children

Table 3
Diagnostic and prognostic value of scalp high-frequency oscillations (HFOs). All studies assessed interictal epochs. Sensitivity, specificity, accuracy, positive and negative predictive value are presented as percentages.

Study	N	# channels	Outcome parameter	Event	Threshold	Sens.	Spec.	PPV	NPV	Acc.	AUC	OR
(van Klink et al., 2016a)	22	21	Epilepsy vs. no epilepsy	S							0.53 (CI 0.29–0.77)	
				R	>2	63	100				0.84 (CI 0.63–0.99)	
			Benign vs. non-benign course	S	>69	100	50				0.85 (CI 0.57–0.98)	
					>399	50	100					
				R	>5	63	100				0.91 (CI 0.67–1)	
(Kramer et al., 2019)	34	10	Active CECTS vs. seizure freedom	S[1]	≥1	100	31	53	100			1.15
				R-on-S[1]	≥1	100	85	83	100			1.65
				S[2]	Largest AUC	100	77	77	100			
				R-on-S[2]	Largest AUC	80	100	100	87			
(Boran et al., 2019)	11	CD: 21[3]	Active focal epilepsy vs. seizure freedom after surgery	R	>0.25/min	80[4]	60[4]	80	60	73 (CI 48–89)		
		LNA: 8[3]		R	>0.25/min	92[4]	67[4]	86	80	84 (CI 62–94)		
(Tamilia et al., 2020)	16	72[3]	Good outcome vs. poor outcome after surgery	S-on-R[5]	≤16 not resected	100[4]	50[4]	77	100	81[4]		
				R-on-S[5]	≤9 not resected	90[4]	83[4]	90	83	88[4]		
(Nariai et al., 2020)	30	20	Active epileptic spasms	Hypsarrhythmia		22	100			40	0.61	
				HFOs[1]	0.51/min	91	100			93	0.98	
				HFOs[2]	1.13/min	83	100			87	0.96	
				R[2]	1.09/min	83	100			87	0.95	
				FR[2]	0.43/min	87	86			87	0.88	
				HFO coupling with 0.5–1 Hz SWA[2,6]	0.27	70	86			73	0.80	
				HFO coupling with 3–4 Hz SWA[2,6]	0.16	74	86			77	0.84	
(Klotz et al., 2021)	56	19[3]	Epilepsy development	S	≥0.045/min	46	70	57	60		0.56 (CI 0.41–0.71)	2.00
				R-on-S	≥0.075/min	38	83	67	61		0.66 (CI 0.51–0.80)	3.13
				R-not-on-S	≥0.125/min	85	90	88	87		0.88 (CI 0.78–0.98)	49.50
			Second seizure	S							0.50 (CI 0.34–0.65)	
				R-on-S							0.59 (CI 0.44–0.75)	
				R-not-on-S							0.88 (CI 0.77–0.98)	

Acc. = accuracy, AUC = area under receiver operating characteristic curve, CD = commercial device, CI = 95% confidence interval, CECTS = childhood epilepsy with centrotemporal spikes, FR = fast ripple (250–500 Hz), G = gamma (30–80 or 40–80 Hz), HFO = high-frequency oscillation (>80 Hz), LNA = low-noise amplifier, NPV = negative predictive value, OR = odds ratio, PPV = positive predictive value, R = ripple (80–250 Hz), S = spike, Sens. = sensitivity, Spec. = specificity, SWA = slow wave activity.
[1] Automatic detection with visual validation.
[2] Automatic detection without visual validation.
[3] The number of used channels was not available, so we reported the number of recorded electrodes.
[4] Calculated based on or derived from text, table or figure by Noorlag et al.
[5] Not resecting spikes-not-on-ripples and not resecting ripples-not-on-spikes were not predictive of outcome.
[6] Quantified by modulation index.

with a first unprovoked seizure (Klotz et al., 2021), and Tamilia et al. and Dorodi et al. children with focal epilepsy (Dirodi et al., 2019; Tamilia et al., 2020). In intracranial EEG, ripples-on-spikes are more specific for the seizure onset zone than ripples-not-on-spikes (van Klink et al., 2014; Lachner-Piza et al., 2020; Wang et al., 2013).

4.2. Limitations

This systematic review was limited by the heterogeneity of the included studies. The 60 studies differed in their study populations, research questions and methods. For example, ten epilepsy types (mostly epilepsy syndromes) are reported in Table 1, and HFO rates were calculated in seven different manners. The variability of HFO rates is partially due to calculation methods, but also depends on characteristics of study populations, EEG recording conditions and HFO analysis methods. Even within patients, HFO rates may vary due to vigilance state and disease activity. There are people who do not fit epilepsy syndrome definitions, and the findings of this systematic review may not apply to them. In addition, sample sizes were small, with a median of 17 individuals (range one to 94) per study, and a few studies evaluated overlapping study populations. For research in general, there is publication bias towards statistically significant results, which may particularly be the case in

this field of research; researchers who do not detect HFOs in their patients will probably not publish this.

HFO research in general, but particularly in scalp EEG, is limited by low signal-to-noise ratio and artifacts. This may cause some EEGs to be too noisy for HFO analysis. HFO amplitude and rate are lower in scalp EEG than in intracranial EEG (Jacobs and Schönberger, 2019). A few studies in this systematic review improved signal-to-noise ratio with tripolar concentric ring electrodes (Besio et al., 2014; Toole et al., 2019), subdermal electrodes (Pizzo et al., 2016b), a low-noise amplifier (Boran et al., 2019) and beamforming (van Klink et al., 2019, 2018), but beamforming can only be used with HD-EEG. Artifacts in the HFO band in scalp EEG are often due to muscle activity, eye movements and external sources, but may also arise due to filtering of sharp EEG events (Bénar et al., 2010). The first can be limited by only assessing epochs during NREM and marking EEG events co-occurring with spikes, and the latter by using optimal filters (such as being developed by Kobayashi et al. (Kobayashi et al., 2021)) and only marking EEG events of at least four oscillations.

Another limitation of HFO research is the challenge to distinguish pathological HFOs from physiological ones. The co-occurrence of HFOs and spikes may help, but no other characteristic (such as frequency or duration) has done this sufficiently to date (Thomschewski et al., 2019). It was previously found in intracranial EEG that NREM early in the night is most suitable to evaluate pathological HFOs, and REM late in the night to evaluate physiological ones (von Ellenrieder et al., 2017). This may not apply for scalp EEG, because Mooij et al. showed that most physiological ripples co-occur with sleep-specific transients (Mooij et al., 2018). Pathological and physiological intracranial HFOs couple differently with scalp SWA in adults with focal epilepsy (Frauscher et al., 2015), but studies in scalp EEG to date only assessed children with epileptic spasms (Bernardo et al., 2020; Kobayashi et al., 2016; Nariai et al., 2020), who also often have an abnormal background pattern (in the context of West syndrome). Two research groups created atlases with normative values for physiological HFOs in intracranial EEG (Frauscher et al., 2018; Kuroda et al., 2021), which may help to distinguish pathological HFOs from physiological ones, but there is no such atlas for scalp EEG yet.

4.3. Recommendations for scalp HFO analysis

When one aims to start HFO analysis in scalp EEG, we recommend to assess interictal epochs during sleep, like most studies in this systematic review did, which helps to minimize the risk of marking artifacts. In addition, the probability to detect pathological HFOs is also higher during sleep than during wakefulness (van Klink et al., 2016a; Klotz et al., 2021; McCrimmon et al., 2021), particularly during NREM early in the night (von Ellenrieder et al., 2017). It is easiest to assess solely HFOs-on-spikes, to minimize the risk of marking artifacts and because most HFOs co-occur with spikes (this systematic review).

Most studies in this systematic review analyzed HFOs in 10–20 EEG in a bipolar montage, but HD-EEG seems better for localization of the presumed EZ (Avigdor et al., 2021; Kuhnke et al., 2018). The number of studies with various montages per epilepsy type was too low to reliably compare them. In general, artifacts are the easiest to circumvent in a bipolar montage, and an average montage is the most suitable for localizing purposes. Combining montages will often yield additional information. The median interictal epoch duration was 12 min, and a recent study showed that 10 min are sufficient to reliably detect scalp HFOs (Cserpan et al., 2021). The probability to detect pathological HFOs is higher in superficial lesions compared with deep ones (Avigdor et al., 2021; Cuello-Oderiz et al., 2017). This probability was not influenced by lesion type in scalp EEG (Cuello-Oderiz et al., 2017), although findings in intracranial EEG contradict each other (Ferrari-Marinho et al., 2015; Jacobs et al., 2009a).

The sample frequency is of the utmost importance; the whole ripple band can be assessed when EEGs are recorded at 1024 Hz, and fast ripples when EEGs are recorded at 2048 Hz, with anti-aliasing filters. Most studies in this systematic review used FIR filters for EEG visualisation. Bénar et al. showed that IIR filters tend to create more oscillatory EEG signals than FIR filters (Bénar et al., 2010). Two studies, however, used IIR filters (McCrimmon et al., 2021; Toole et al., 2019), one to reduce calculation time of automatic detection (McCrimmon et al., 2021).

Visual detection is still the gold standard for HFO analysis. Its subjectivity is considered an important limitation, but six studies in this systematic review found favorable intra- and interrater reliability. Interrater reliabilities of spikes and HFOs are more or less comparable in intracranial and scalp EEG (Cao et al., 2019; Nariai et al., 2018; Zelmann et al., 2009). Automatic detection in scalp EEG has been on the rise since 2012 (von Ellenrieder et al., 2012), and recently the first studies without visual validation have been published (Kramer et al., 2019; McCrimmon et al., 2021; Nariai et al., 2020). Fully automatic detection would avoid any subjectivity and drastically reduce detection time. Kramer et al., however, reported a decrease in detectability from 97% before validation to 33% after validation (Kramer et al., 2019), and we thus recommend combining automatic detection with visual validation. Visual detection, but also visual validation, is more time-consuming than fully automatic detection, and this may threaten applicability. A few automatic detectors for scalp HFOs have been made public (Boran et al., 2019; Chu et al., 2017; Gerner et al., 2020; Kramer et al., 2019; Nariai et al., 2020), but future studies are needed to establish whether they work sufficiently in all study populations (children vs. adults; all epilepsy syndromes), and in all EEG recordings with variable signal-to-noise ratio within one study population.

4.4. Gaps of knowledge and future directions

There are still many questions to be answered. A minority of studies in this systematic review analyzed fast ripples (Bernardo et al., 2020, 2018; Charupanit et al., 2018; Nariai et al., 2018; Pizzo et al., 2016b), while fast ripples in intracranial EEG seem to have a higher value for localizing the EZ than ripples (van 't Klooster et al., 2017), and physiological fast ripples are rare (Frauscher et al., 2018). Fast ripples are even smaller EEG events than ripples, and thus even harder to detect due to scalp EEG's low signal-to-noise ratio. To date, no physiological fast ripples in scalp EEG have been described. Future studies are needed to establish the clinical value of fast ripples in scalp EEG.

Age dependency of scalp HFOs could be further explored. Findings in this systematic review were contradictory (Klotz et al., 2021; Kobayashi et al., 2009; Ohuchi et al., 2019; Tsuchiya et al., 2020), but a recent study (published after the date of our systematic search) reported a higher ripple rate in children younger than seven years compared to older ones (Cserpan et al., 2021). The thickness of the skull may also play a role in scalp HFOs, since pathological HFOs have recently been found in a premature neonate (Noorlag et al., 2021). It would be interesting to systematically study from which age onwards pathological and physiological HFOs can be generated, their correlation with brain development, and whether their clinical value is different in the young compared to the elderly. Ripples in childhood epilepsy may not have a simple linear relation with age, but a complex correlation with age-dependent appearance and disappearance of epilepsy syndromes.

Klotz et al. showed that HFOs arose before epilepsy development in children with a first unprovoked seizure (Klotz et al., 2021). Another question to be answered is whether HFOs also arise

before seizure development, like in rats (Bragin et al., 2000). Suitable study populations may be adults after brain trauma, neonates with thalamic injury or children with tuberous sclerosis complex; all because of the high risk of eventual epilepsy development (Christensen et al., 2009; van den Munckhof et al., 2020; Nabbout et al., 2019).

Three studies evaluated physiological HFOs (two in the same study population) (Gerner et al., 2020; Mooij et al., 2018, 2017), and a few others described presumably physiological HFOs in areas outside the presumed EZ or in controls (Dirodi et al., 2019; McCrimmon et al., 2021; Nariai et al., 2020; Tamilia et al., 2020). It would be interesting to further study the correlation of physiological scalp HFOs with cognition, and the possible confounding effect of pathological HFOs. Such a correlation has been suggested for hippocampal HFOs in rats (Maingret et al., 2016), and recently for scalp ripples in children with neurodevelopmental disorders (Oka et al., 2021).

Finally, HFOs have mostly been studied in epilepsy, and it would be interesting to enlarge the field of HFO research to other neurological disorders; for example, to study whether HFOs play a role in the high co-occurrence of epilepsy and migraine (Keezer et al., 2015). For all aforementioned topics, it would be relevant to conduct multicenter studies, to improve generalizability of findings.

5. Conclusions

This systematic review described 60 studies with data from 1149 unique individuals. The methodologies of the included studies were heterogeneous, but pathological HFOs in scalp EEG have localizing, diagnostic and prognostic value, particularly in children with epilepsy, and we believe their clinical potential thus extends beyond the field of epilepsy surgery. Future studies should use more homogeneous methods to improve comparability and applicability.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Author contributions

All authors contributed to the conception of the systematic review; LN performed the step-by-step selection and data extraction, supervised by MZ; LN made the tables and figures, supervised by MZ; LN wrote the first draft of the manuscript; all authors contributed to the writing of the manuscript, and approved the final version.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clinph.2021.12.017.

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