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Interictal epileptiform discharges vary across age groups

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HIGHLIGHTS

- Focal interictal epileptiform discharge (IED) morphology changes with age.
- The distribution of quantitative IED measures by age needs to be considered in EEG interpretation.
- IEDs are consistently asymmetric across all age groups.

ABSTRACT

Objective: To investigate whether the occurrence and morphology of interictal epileptiform discharges (IEDs) in scalp-EEG change by age.
Methods: 10,547 patients who had a standard or sleep deprived EEG recording reported using the SCORE standard were included. 875 patients had at least one EEG with focal IEDs. Focal IED morphology was analyzed by age using quantitative measures in EEGLAB and by visual classification based on the SCORE standard. We present distributions of IED measures by age group, with medians, interquartiles, 5th and 95th percentiles.
Results: Focal IEDs occurred most frequently in children and elderly. IED morphology and localization depended on age ($p < 0.001$). IEDs had higher amplitudes, sharper peaks, larger slopes, shorter durations, larger slow-wave areas and wider distributions in children. These morphological characteristics diminished and the IEDs became more lateralized with increasing age. Spike asymmetry was stable across all age groups.
Conclusions: IEDs have age-dependent characteristics. A spike detector, human or computer, should not operate with the same set of thresholds for patients at various age. With increasing age, focal IEDs are less sharp, have lower amplitudes, have less prominent slow-waves and they become more lateralized. Our findings can help EEG readers in detecting and correctly describing IEDs in patients of various age.
Significance: EEG readers should always consider patient age when interpreting interictal epileptiform discharges.

1. Introduction

Interictal epileptiform discharges (IEDs) represent a highly relevant finding in EEG (Bouma et al., 2016; Krumholz et al., 2015; Koutroumanidis et al., 2017). IEDs are usually described in general and descriptive terms without any quantitative definitions (Sannit and Lilienthal, 1962; Chatrian et al., 1974; Noachtar et al., 1999; Kane et al., 2017). Simple metrics such as amplitude, duration and sharpness could be easily obtained, but are not utilized in clinical practice. Clinical experience indicates that IEDs tend to be blunter in the elderly, but there is little data to corroborate this. No studies have looked at quantitative measures of focal IEDs by age.

Localization and frequency of occurrence of IEDs and other focal EEG abnormalities depend on age (Hughes, 1967; Koufen and Gast, 1981). IED morphology and localization may also be influenced by age for well-defined epilepsy types or specific syndromes (Aurlien et al., 2007; Konishi et al., 1994; Sadleir et al., 2009; Lee et al., 2010), but this has not been systematically examined. Aurlien et al. (2009) showed that the amplitude of generalized epileptiform activity changed with age, while the frequency of the discharges did not.

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Analytical methods and classification of EEG activity vary in the previous studies. The SCORE standard has been adopted to reduce EEG interpretation variability, and to improve clinical and scientific studies (Beniczky et al., 2017), but so far only sparse data has been published on the basis of SCORE. Detection of IEDs by ordinary visual analysis has less than optimal reproducibility (van Donselaar et al., 1992; Stroink et al., 2006). IED detection is also subject to overinterpretation of non-epileptiform EEG graphoelements as IEDs (Benbadis and Thomas, 2017), and depends on only a few aspects of quantitative IED morphology (Bagheri et al., 2017). More detailed knowledge of how IEDs change by age should improve clinical EEG interpretation in the individual patient and lead to more precise age-dependent spike detection algorithms.

IEDs are defined as transient activity distinguishable from the background activity and with a characteristic morphology typically, but neither exclusively nor invariably, found in interictal EEGs of people with epilepsy (Kane et al., 2017). Six morphological criteria are given, out of which four have to be met in order to classify a graphoelement as IED. IEDs should contain:

(1) Di- or tri-phasic waves with sharp or spiky morphology (i.e. pointed peak).
(2) Wave-duration different from the ongoing background activity, either shorter or longer.
(3) Waveform asymmetry: a sharply rising ascending phase and a more slowly decaying descending phase, or vice versa.
(4) The transient should be followed by an associated slow after-wave.
(5) The background activity surrounding epileptiform discharges should be disrupted.
(6) Distribution of the negative and positive potentials on the scalp should suggest a brain source of the signal, corresponding to a radial, oblique or tangential orientation.

The exact sensitivity and specificity of each criterion for IEDs is not known. Descriptors for criterion 1 (spike and sharp wave morphology) and 4 (presence of slow-wave), are included in the SCORE terminology.

The aim of this study was to investigate how the occurrence and morphology of IEDs change with age in a large and unselected cohort of patients with epilepsy. Precise, age-dependent criteria for IED should improve diagnostic specificity and individualized treatment in epilepsy.

2. Methods

2.1. Patients

We included all consecutive patients who had standard EEGs or sleep deprived EEGs recorded at Haukeland University Hospital during the period March 4th, 2013 - October 29th, 2017, and which were reported in SCORE EEG (13143 EEGs, 10,547 patients, Fig. 1). One EEG was selected for each patient. For the 2596 patients who had recorded two or more EEGs the first EEG with a diagnostic conclusion of epilepsy and epileptiform findings was chosen. If the patient had no such EEG the last EEG recording was chosen. We used the diagnostic conclusion in the clinical EEG report produced in SCORE to further categorize patients. This diagnostic conclusion was drawn by the EEG interpreter from the EEG findings together with available clinical and paraclinical information. A diagnostic conclusion of epilepsy required a clinical suspicion of epilepsy written on the referral and epileptiform activity in the EEG. 9238 patients had a diagnostic conclusion other than epilepsy in their EEG report and served as a control group when assessing demographic characteristics.

1309 patients had at least one EEG with epileptiform findings and a diagnostic conclusion of epilepsy. The first EEG with epileptiform activity for each patient was selected for analysis. The groups with *focal* ($N = 875$), *generalized* ($N = 207$) and *unspecified* ($N = 227$) epilepsy type were analyzed separately, compared to controls, and analyzed by age. The *unspecified* group consisted of patients who had a diagnostic conclusion of either "epilepsy not further specified" ($N = 152$), an epileptic seizure during the EEG recording ($N = 27$), a hypsarrhythmia pattern ($N = 2$), or where the EEG report had conflicting data, e.g. included both focal and generalized epilepsy in the diagnostic conclusion ($N = 46$). The diagnostic conclusion included a suggestion of probable *etiology* of the patient's epilepsy, whether *symptomatic*, *idiopathic* or *undetermined*. Etiology was used as a control variable in multiple linear regression described in Section 2.5. IED morphology was visually and quantitatively analyzed by age and IED localization was visually analyzed in the focal epilepsy group. The patients were grouped by age in years into ten groups: <1 year, 1–9 years, 10–19 years, 20–29 years, 30–39 years, 40–49 years, 50–59 years, 60–69 years, 70–79 years and 80–101 years.

2.2. EEG recording

Electrodes were applied according to the 10–20 system with a minimum of 21 and a maximum of 25 electrodes. When possible, EEGs were recorded with the patients in a supine, relaxed position with their eyes closed. For sleep deprived EEGs, adults were deprived of a whole night's sleep before the recording, while children were kept awake since 3am. the same morning. Patients were encouraged to sleep during the recording. Provocation by hyperventilation and photic stimulation was carried out unless contraindicated. Nicolet™ EEG system was used to record and display EEGs. Average montage with paper speed 3 cm per second and 1 cm per 100 μV was the default setup for review. Montage, sensitivity and paper speed could be adjusted freely by the EEG reader.

2.3. IED morphology

2.3.1. Visual analysis

Morphological categories for IEDs were determined according to the SCORE standard as spikes, spike-and-slow-waves, sharp-waves, sharp-and-slow-waves, polyspikes, polyspike-and-slow-waves, and slow-sharp-waves (Beniczky et al., 2017). Multiple morphologies could be selected for each finding. The patients were divided into two groups depending on whether their EEG contained any IEDs with spike morphology or not. Patients were also divided into two groups depending on whether their EEG contained any IEDs with a slow-wave or not.

2.3.2. Quantitative analysis

The first IED finding in each EEG was chosen for quantitative analysis. All EEGs were digitally filtered using the EEGLAB function pop_eegfilt with a high pass filter at 1 Hz, low pass filter at 70 Hz and a notch band filter spanning 48–52 Hz (Delorme and Makeig, 2004). The electrode or channel in average montage where the IED was most convincingly epileptiform was selected. Spike start, spike peak, spike end and slow-wave end was manually annotated by the first author for all EEGs using custom software built on EEGLAB (ScorePipeline, available from the authors on GitHub (Brøgger, 2019), Fig. 2). Voltage sensitivity and time axis could be adjusted freely for optimal annotation placement. Spike start was marked at the maximal positive time point in the trough leading into the spike. Spike peak was marked at the negative maximum following spike start. Spike end was marked at the maximal positive component following spike peak. If a slow-wave followed, spike end marked its start, and another mark was set at the end

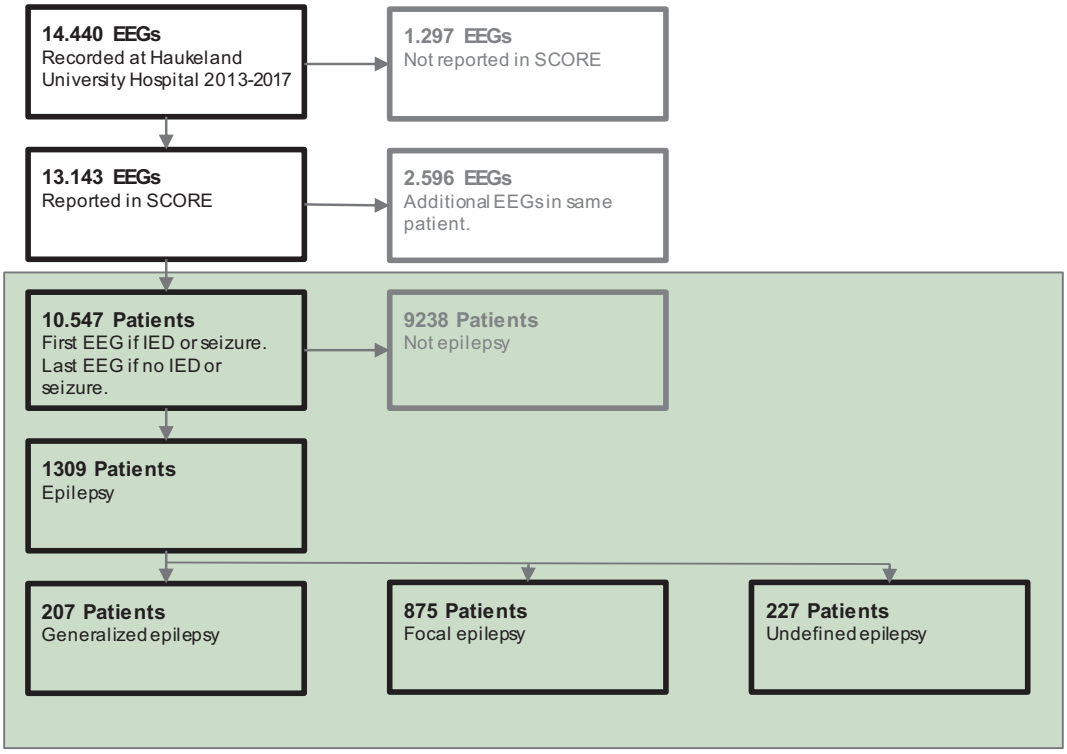

Fig. 1. Patient and EEG flow chart with included and excluded groups.

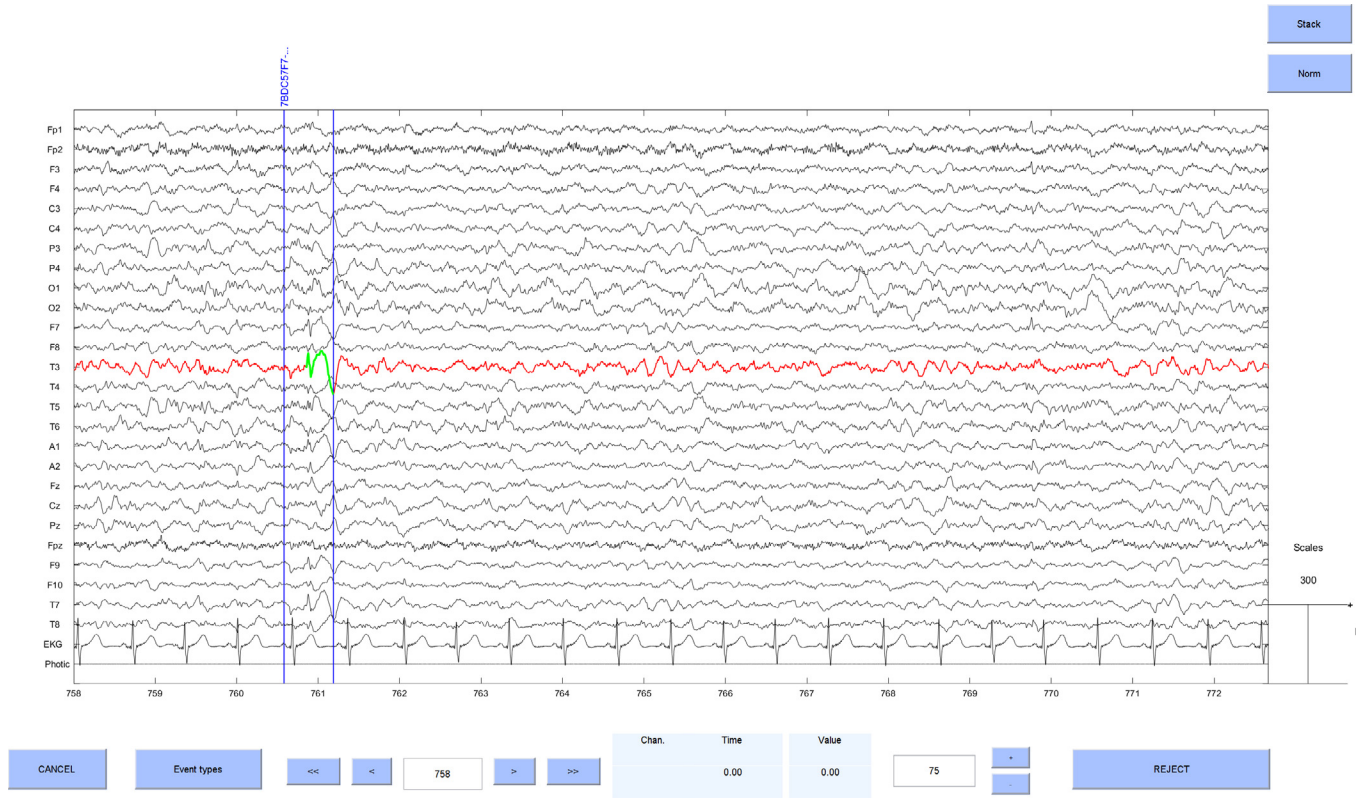

Fig. 2. Manual annotation of an IED in ScorePipeline. Green: Annotation in progress. Leftmost vertical blue line: An EEGLAB event marker. Rightmost vertical blue line: Mouse cursor position on the x-axis. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

of the slow-wave. The first half-wave was defined as the sample points between spike start and spike peak. The second half-wave was defined as the sample points between spike peak and spike end. The following quantitative measures were derived from these time points.

2.3.2.1. Sharpness. Approximation D of the $d^2\mu V/dt^2$ value around spike peak according to Frost (1979). Five sample points were obtained at fixed distances from spike peak ($t = 0$ ms), where $N_1 = t - 8$ ms, $N_2 = t - 4$ ms, $N_3 = t - 0$ ms, $N_4 = t + 4$ ms, $N_5 = t + 8$ ms. Then $D = (N_5 - 2*N_3 + N_1)/2$. Values are greater than 0. A greater value corresponds to a sharper spike peak.

2.3.2.2. Ascending slope. Ascending amplitude (μV) divided by the duration of the first half-wave. Values are greater than 0. A greater value corresponds to a steeper ascending slope.

2.3.2.3. Descending slope. Descending amplitude (μV) divided by the duration of the second half-wave. Values are greater than 0. A greater value corresponds to a steeper descending slope.

2.3.2.4. Ascending amplitude. Voltage difference (μV) between spike peak and spike start. Values are greater than 0. A greater value corresponds to a larger amplitude of the first half-wave.

2.3.2.5. Descending amplitude. Voltage difference (μV) between spike peak and spike end. Values are greater than 0. A greater value corresponds to a larger amplitude of the second half-wave.

2.3.2.6. Duration. Milliseconds from spike start to spike end. Values are greater than 0. A greater value corresponds to a broader spike component of the IED.

2.3.2.7. Area of slow-wave. A Gaussian wave was fitted to the time series segment defined as the slow-wave using MATLAB's *fit* function (MATLAB). The signal was shifted so that the positive maximum was at baseline (0 μV). The trapezoidal integral, defined by the start and end point of the slow-wave, was then subtracted from the area of the fitted Gaussian to give the estimated area of the slow-wave in μV*second (weber, a unit derived from the International System of Units). Values are positive, zero, or negative. A greater positive value corresponds to a larger slow-wave area. Negative values can result from a poor model fit.

2.3.2.8. Spike asymmetry. Duration of the first half-wave divided by the duration of the second half-wave as defined by Henze et al. (2002). Values are real numbers greater than 0. A value less than 1 corresponds to a shorter duration of the first half-wave compared to the second half-wave. A value greater than 1 corresponds to a longer duration of the first half-wave compared to the second half-wave.

To provide a visual reference for EEGers, an average IED was calculated from the raw EEG signal for each age group. The IEDs were averaged centered on the spike peaks as time zero. 95% confidence intervals were calculated for each age group from 10,000 bootstrap samples.

2.4. IED localization

IED visual localization was examined on a regional level where each electrode containing IEDs was assigned to one out of thirteen topographical brain regions *frontal (left/midline/right)*, *central (left/midline/right)*, *temporal (left/right)*, *parietal (left/midline/right)* and *occipital (right/left)*. Ordinal categories were used for multiple linear regression, with regions *frontal, temporal, central, parietal and occipital*, and laterality *left*, *right* and *other*. IEDs were classified as *frontal* if regional localization included the frontal region. Remaining observations were successively classified as *temporal*, *central*, *parietal* and *occipital*. IEDs were classified as *left* if localized strictly to the left hemisphere and/or midline, as *right* if localized strictly to the right hemisphere and/or midline, or as *other*.

2.5. Statistics

Pearson's chi-squared test was used to examine the association between age and epilepsy type and IED morphology, and multiple logistic regression to test age dependency for IED localization. The non-parametric Kruskal-Wallis-test was used to examine age dependency for quantitative IED measures (sharpness, ascending slope, ascending amplitude, duration, spike asymmetry, area of slow-wave). We performed linear regression of the IED quantitative measures (sharpness, ascending slope, ascending amplitude, duration, slow-wave area) as the dependent variable and age, etiology, region and laterality as independent variables, in order to control for the possible effect of location. A *p*-value threshold of $p < 0.01$ was chosen due to the numerous comparisons that were undertaken.

2.6. Software

Nicolet™ EEG system was used to record and display EEGs for visual analysis. Clinical EEG reports were made with SCORE EEG (versions 1.0.9.4012 to 2.9.16.24). All EEG reports were stored in the SCORE database, a structured SQL database. Quantitative annotation was implemented in custom software built on EEGLAB. All statistics were handled in Stata. Scripts will be made available on GitHub (Brøgger and Aanestad, 2019).

2.7. Ethical approval

The study was approved by the Regional Committees for Medical and Health Research Ethics (reference code 2017/1512/REK vest).

3. Results

3.1. Demography

The mean age of all 10,547 included patients was 35 years, and 48.9% were females (Table 1). The occurrence of both epilepsy and epilepsy type depended on gender ($p < 0.01$ and $p < 0.001$, respectively).

3.2. Epilepsy type

Epilepsy type depended on age ($p < 0.001$, Fig. 3). Focal epilepsy was the most common type in all age groups, with the highest occurrence in children and elderly people. Generalized epilepsy had its peak in adolescence. The age groups 20–29 and 30–39 years had the lowest occurrence of epilepsy.

Table 1
Demographic characteristics of patients included in the study.

	N=	Female % (95% CI)	Age in years mean (SD)
Diagnosis			
Epilepsy	1270	52.5 (49.8–55.3)	35.3 (28.3)
No epilepsy	8971	48.4 (47.4–49.4)	34.8 (25.3)
Total	10,241	48.9 (47.9–49.9)	34.9 (25.7)
Epilepsy type			
Generalized	198	65.2 (58.2–71.5)	22.8 (16.3)
Focal	850	49.8 (46.4–53.1)	40.1 (30.3)
Other	222	51.8 (45.2–58.3)	28.1 (28.3)

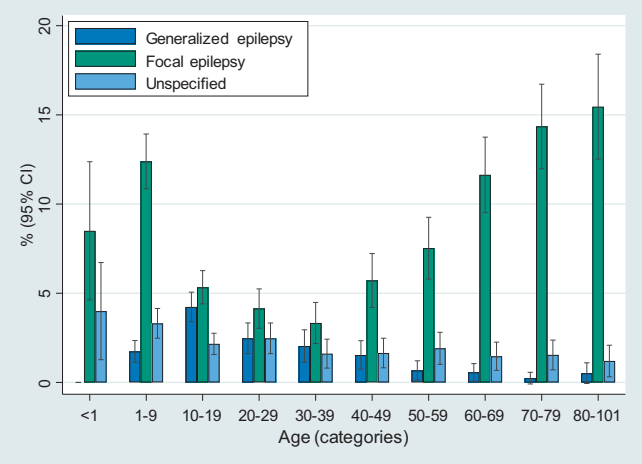

Fig. 3. Occurence of generalized, focal and unspecified epilepsy, by age, in patients referred for standard or sleep-deprived EEG ($N = 10547$).

3.3. IED morphology by age

The average time series by age illustrate trends in quantitative measures (Fig. 4 and Supplementary Figure 1). The various measures of IED morphology showed that IEDs became blunter with increasing age, and also that slow-waves became less pronounced (Fig. 5A–F). Spike sharpness, slope, amplitude, duration and slow-wave area all depended on age ($p < 0.001$, Table 2).

3.3.1. Age trends by visual classification

The occurrence of spikes and slow-waves both depended on age when examined by visual analysis ($p < 0.001$ and $p < 0.001$. Fig. 5A). Spikes and slow-waves were more often reported in the younger age groups (Fig. 5A). In the age groups 1–19 years, 70% of focal spikes were classified as having a following slow-wave, whereas this was the case for only 30% above age 80 years.

3.3.2. Spike sharpness

Spike sharpness, measured as the approximation $D = d^2V/dt^2$ around the peak, had its maximum in infancy with median $D = 4.5$. It then declined slowly with increasing age to a minimum with median $D = 2.0$ above age 80 years. A sharpness of $D = 1$ was in the 10th percentile below age 70 years. A sharpness of $D = 6$ was in the 75th percentile at age 0–9 years, but in the 90th percentile or above in patients older than 9 years. The distribution of sharpness was wider below age 10 than above.

3.3.3. Spike slope

Ascending and descending slopes were increasingly steep during the first decade of life, up to a median 2.5 μV/ms in the age group 1–9 years, but then gradually less steep with a further increase in age, down to a median of 1 μV/ms. Slopes of 1 μV/ms were in the 5th percentile in age groups 1–19 years, while in the 25th percentile or higher for other age groups. Slopes of 3 μV/ms were in the 75th percentile in age groups 0–19 years, and in the 90th percentile or higher at ages above 20 years. The distribution of spike slopes was wider below age 10 than above, and declining with age.

3.3.4. Spike amplitude

Spike ascending amplitude had a similar age distribution as spike slopes, with an increase from infancy to early childhood up to a median of 100 μV in age group 1–9 years, and then a gradual decline to a median of 60 μV. An ascending amplitude of 40 μV was in the 25th percentile or lower for all age groups. 100 μV was in the 75th percentile at age 0–19 years, while in the 90th per-

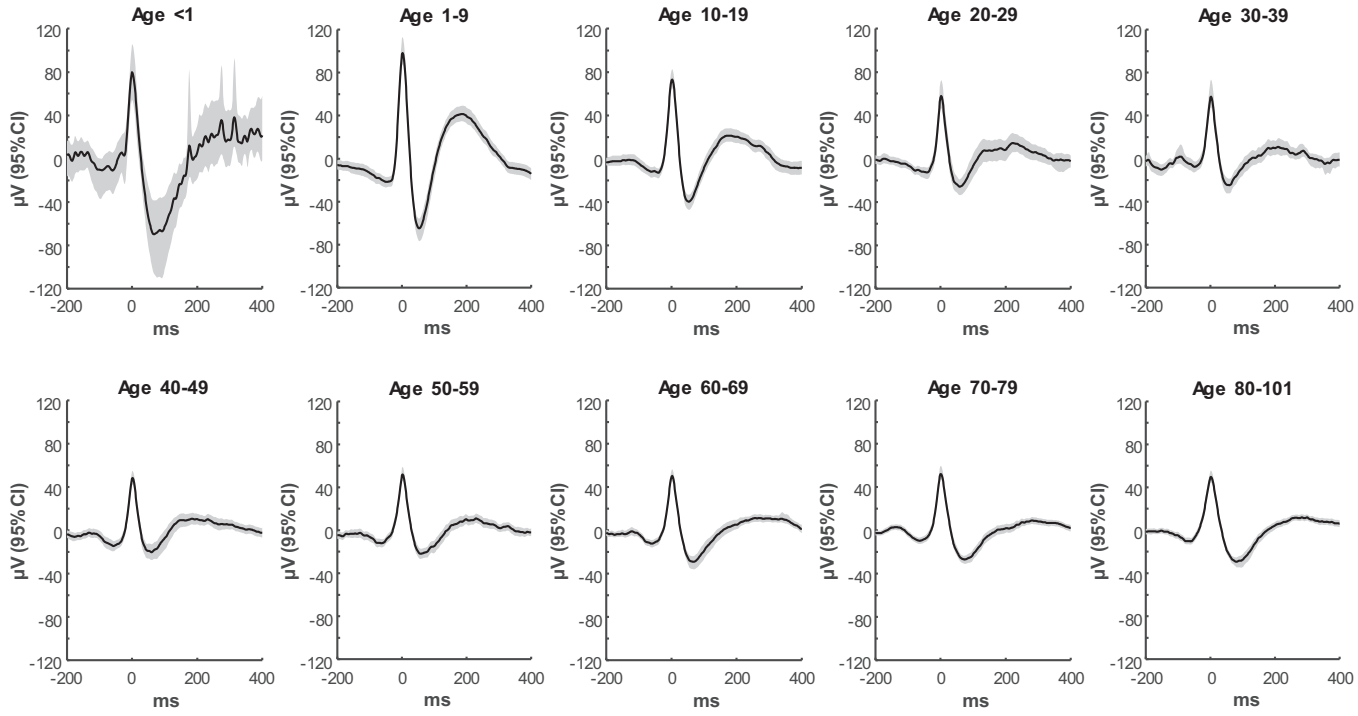

Fig. 4. Average IED time series in focal epilepsy by age categories in years. 95% confidence levels are shown by shaded grey area (barely visible for most age groups). The average was calculated with spike peak defined as time = 0 ms, from 200 ms before until 400 ms after the spike peak, at the electrode where the IED was most convincingly epileptiform ($N = 868$).

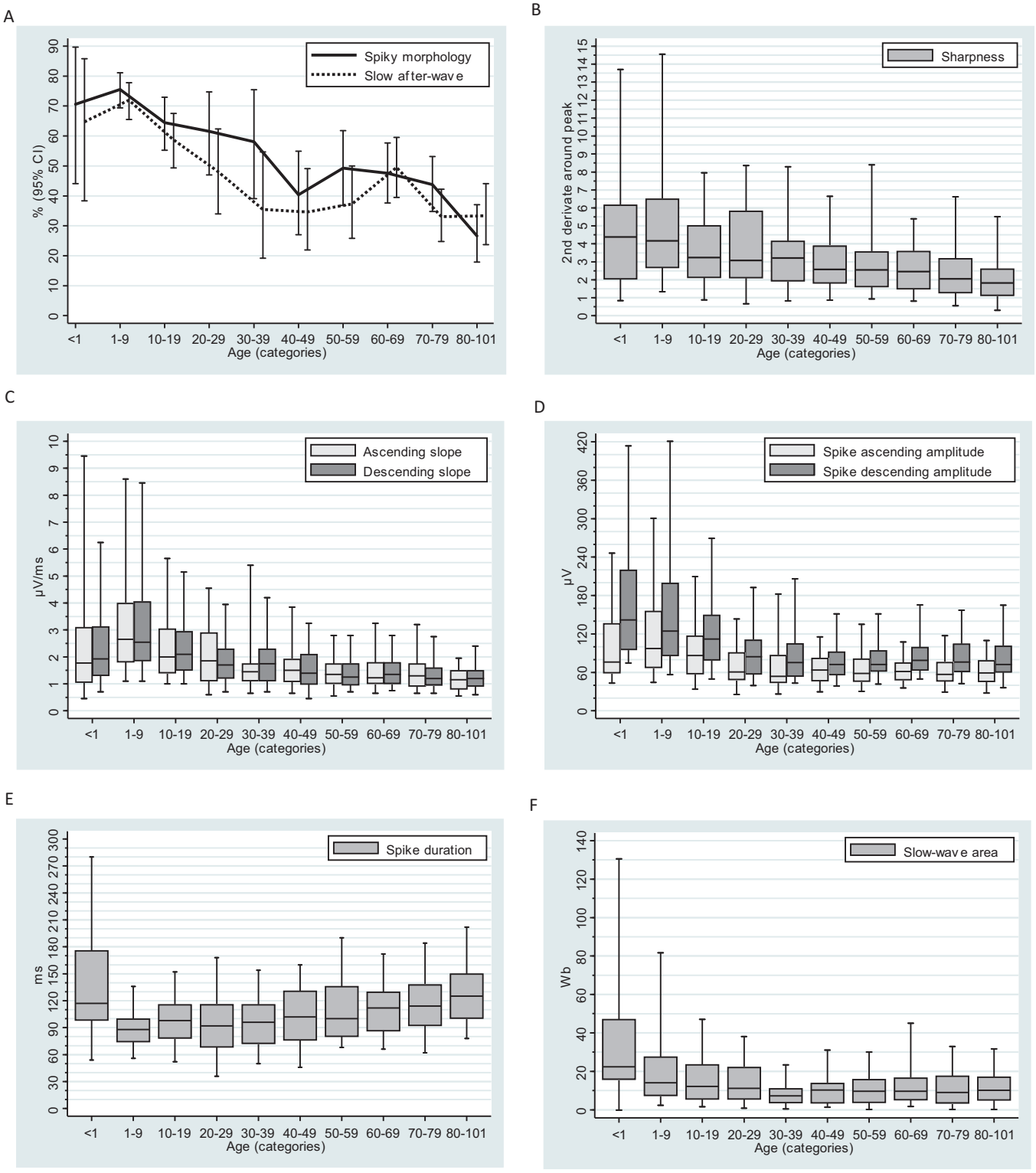

Fig. 5. Morphology and quantitative measures of IEDs by age categories (years). Occurrence is given by percentage with a 95% confidence interval for morphology classified by visual interpretation (A). Median, interquartile range, 5th percentile and 95th percentile is given for the quantitative measures (B–F). A: Occurrence of spikes and slow-waves components in morphological descriptors of IED according to visual analysis with SCORE in focal epilepsy by age. (*N* = 875). B: Sharpness of the IED spike component around peak (*N* = 868). C: Ascending and descending slope of the IED spike component in µVolt per ms (*N* = 868). D: Ascending and descending amplitudes of the IED first and second half waves (*N* = 868). E: Duration of the IED spike component in milliseconds (*N* = 868). F: Area of the slow-wave in weber (*N* = 868).

centile or higher above age 20. Spike descending amplitude was larger compared to the ascending amplitude for all age groups. It had a maximum of 140 µV in infants, then a gradual decrease, before stabilizing at 80 µV for all age groups 20–101 years. The distribution of spike amplitudes was wider below age 10 than above.

3.3.5. Spike duration

Spike duration decreased from early infancy to a minimum median of 90 ms in early childhood. Then it gradually increased with age to a median of 130 ms. Spike duration < 60 ms was in the 5th percentile above age 50 years. A spike duration of > 200 ms

Table 2
Regression model for quantitative IED measures by EEG region, laterality and age category (years).

	Sharpness		Slope		Amplitude		Duration (ms)		Slow-wave area	
	Coef. (μV/ms2)	*p*-value	Coef. (dμV/ms)	*p*-value	Coef. (μV)	*p*-value	Coef. (ms)	*p*-value	Coef. (weber)	p-value
Base value		<0.001		<0.001		<0.001		<0.001		<0.001
Constant	5,8		7,3		141		98,6		32,3	
Region		0,02		0,08		0,29		0,94		<0.01
Frontal	(Reference category)									
Temporal	−0,8		−0,9		−7,6		0,7		−4,5	
Central	−1		−0,9		−18,8		2,7		−8,3	
Parietal	−0,1		−0,1		0		1,9		−4,1	
Occipital	0,9		0,6		1,8		−6,9		−7,2	
Laterality		<0.01		<0.001		0,01		<0.001		0,02
Left	(Reference category)									
Right	0,5		0,8		9,6		2,8		2,3	
Other	0,8		1,2		17		−8,7		4,4	
Etiology		0,04		<0.01		<0.001		<0.01		<0,001
Idiopathic	−1,1		−1,2		−16,2		−4,3		−13,2	
Symptomatic	(Reference category)									
Undetermined	−0,4		−0,9		-22		−9,6		−9,4	
Age category		<0.001		<0,001		<0,001		<0,001		<0,001
<1	−1,6		−2,7		−35,3		55,6		6,6	
1–9	(Reference category)									
10–19	−1,7		−2,2		−40,5		7,6		−10,9	
20–29	−1,9		−3,2		−66,3		−1,1		−14,8	
30–39	−2,8		−4,4		−76,5		4,8		-22,3	
40–49	−2,8		−4,2		−75,6		8,0		−20,5	
50–59	−2,6		−4,4		−71,5		16,9		−19,9	
60–69	−3		−4,4		−77,2		15,4		−16,8	
70–79	−3,1		−4,5		−76,9		19,1		−19,2	
80–101	−3,9		−5,2		−79,7		35,3		−19,9	
Adjusted R-squared	0,14		0,19		0,16		0,14		0,15	

was in the 90th percentile in infants < 1 year old, and in the 95th percentile or above for all ages 1–101 years. The distribution of spike durations was wider below age 1 years than any other age, then reached a minimum at ages 1–9 years.

3.3.6. Slow-wave

The slow-wave area was largest and most variable in infancy with median 20 weber. It decreased during early childhood to a median of 15 weber, but with substantial variability for age group 1–9 years. It then stabilized at a median of around 10 weber for the age groups 10–101 years. Slow-waves with an area of 50 weber were in the 90th percentile at age 0–9 years, and in the 99th percentile or higher for ages above 10 years.

3.3.7. Spike asymmetry

Spike asymmetry had a median around 0.8 for all groups and did not depend on age (results not shown in Fig. 5).

3.3.8. Regression model

Multiple linear regression models for quantitative IED measures by brain region, laterality, etiology and age, showed that age had the strongest effect on all of these measures (Table 2). Idiopathic and undetermined etiology had a subtractive effect on spike slope, spike amplitude, spike duration and slow-wave. For ease of interpretation the percent changes in age coefficients are shown in Fig. 6. The oldest patient group had the most pronounced change for all quantitative measures, and the coefficient change from the base value ranged from 36% to 72%. The only exception was for slow-wave area.

3.4. Localization of focal IEDs

IED localization depended on age for most brain regions ($p < 0.001$). The exceptions were the right frontal, right temporal and left parietal regions (Fig. 7). IEDs became more lateralized with increasing age. The occipital and central regions rarely showed

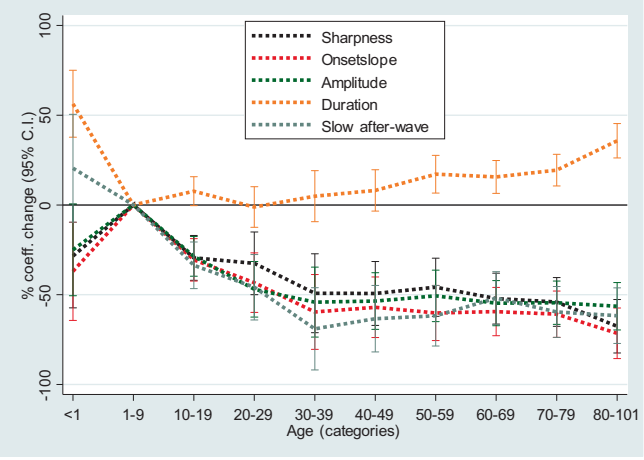

Fig. 6. Percent change in the coefficient size of age (years) from a linear regression of quantitative IED measures by age adjusted for brain region, laterality and etiology. The age group 1–9 years was used as reference in the regression model.

IEDs in elderly patients. IEDs were increasingly common over the left hemisphere with increasing age.

4. Discussion

We have shown that the morphology of IEDs depends on age. Focal IEDs become more common with age, and their quantitative characteristics change. With increasing age IEDs appear less sharp, have lower amplitudes, have less prominent slow-waves, and their scalp localization becomes more lateralized. They also occur more frequently over the left hemisphere. Spike asymmetry was our only IED measure that did not vary by age, and this IED criterion applies evenly for all ages. Our findings can help EEG readers in detecting and correctly describing IEDs in patients of various age.

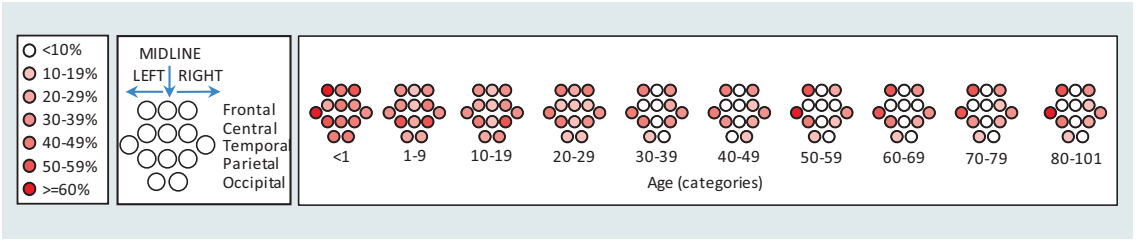

Fig. 7. Regional occurrence of IEDs by age (years) as scored by visual analysis (N = 844). One head model is shown for each age group. Circles represent EEG regions. Intensity of red indicates the percentage of IEDs that occurred in the corresponding region and age group.

Guidelines for classifying IEDs do not include quantitative criteria, and no provision has been made for changes in the criteria with age. Our data provide such quantitative characteristics to guide the EEGer in IED detection and classification. All quantitative measures falling outside the 5th or 95th percentile of these age distributions should be interpreted cautiously to avoid false positive IED detection. For example, if an EEG reader is contemplating whether a sharp wave with ascending slope of less than 1 μV/ms represents an IED in a 15 year old patient, this would be a rare IED event. The possibility that the wave instead represents an artifact or a physiological waveform should be examined more closely. On the other hand, if the patient was 90 years old, the ascending slope would be well within the interquartile range and even close to the median value for the corresponding age group. It is apparent from our findings that the spike detector, human or computer, cannot operate with the same set of thresholds for patients of various ages. Furthermore, the observed differences imply that the sensitivity and specificity in IED detection might not be the same across age groups.

IEDs with a duration of less than 35 ms were infrequent in our material, while IEDs with a duration greater than 200 ms were seen occasionally, mostly in the very young and very elderly. No limits for the duration of IEDs are given in the definition of epileptiform activity. Spikes and sharp waves are defined separately as epileptiform transients with a duration of 20 to less than 70 ms and 70 ms to 200 ms respectively, effectively rendering a portion of the IEDs in our material unnamed. The glossary of terms should not exclude IEDs by arbitrary limitations.

Despite blunted and low amplitude IEDs, the oldest age group had the highest occurrence of focal IEDs. The prevalence of epilepsy is higher in the elderly (Beghi and Giussani, 2018), but the sensitivity of EEG decreases with age as the occurrence of IEDs in elderly with epilepsy is less frequent than in younger patients (Drury and Beydoun, 1998). A higher signal-to-noise ratio due to lower background activity power in older patients (Dustman et al., 1999) makes their IEDs stand out more. Life expectancy is increasing and the oldest segment of the population is expanding (Christensen et al., 2009). To diagnose epilepsy and detect IEDs with sufficient sensitivity and specificity in elderly patients will be of even greater importance in the future and needs special attention in diagnostic workup.

The quantitative IED measures are not independent variables. They are mostly measures of the same triangular-like shape that constitutes the spike. Still, each measure represents visually distinct and meaningful properties of the IED. The measures display a similar percent wise change by age when controlled for IED localization, laterality and etiology. No attempt was made to explain if, and how, one quantitative IED measure predicts another. The aim of this study was rather to test the hypotheses that IED morphology and IED occurrence change with age, which were confirmed for both.

We included all EEGs examined at our department for this study, not excluding those with referral reasons other than a suspicion of epilepsy. 63% of the patients were referred with an indication related to epilepsy (data not shown). This included patients for whom the epilepsy diagnosis had not yet been established, and those with an established diagnosis where monitoring or follow-up was requested to guide therapy. The occurrence of epilepsy had a bimodal distribution with two peaks, one at age 1–9 years and another at 80–101 years. Our laboratory is the only EEG provider in our region, and so our material consisted of an unselected and complete EEG patient population referred from a wide range of general practitioners and specialists.

This is a cross-sectional study. We annotated only the first IED of the first epileptiform EEG for each patient, which may not have been the most prominent or informative. Variability of IEDs within the same EEG occurs, but was not examined in this study. Our regression model might have better explained the quantitative IED measures with access to variables such as background activity power, patient medication, intracranial imaging data and seizure frequency. Decreasing general EEG amplitude with age is a known phenomenon (Dustman et al., 1999), and this may influence the amplitude also of IEDs.

5. Conclusions

Focal IEDs occurred most frequently in children and elderly. IEDs have age-dependent characteristics. With increasing age, focal IEDs appeared less sharp, had lower amplitudes, and had less prominent slow-waves. With increasing life expectancy these changes in IED morphology have increasing relevance. A spike detector, human or computer, should not operate with the same set of thresholds for patients at various ages.

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Declaration of Competing Interest

Jan Brøgger and Eivind Aanestad are minority shareholders in Holberg EEG AS, the providers of the SCORE EEG software used in this study. Nils Erik Gilhus declares no conflicts of interest.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clinph.2019.09.017.

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