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Postictal EEG changes following focal seizures: Interrater agreement and comparison to frequency analysis

Ivan C. Zibrandtsen [a,*], Sigge Weisdorf [a], Martin Ballegaard [a], Sándor Beniczky [d], Troels W. Kjaer [a,b,c]

[a] Department of Neurophysiology, Zealand University Hospital, Roskilde, Denmark
[b] Department of Clinical Medicine, University of Copenhagen, Denmark
[c] Department of Neuroscience, University of Copenhagen, Denmark
[d] Department of Clinical Neurophysiology, Danish Epilepsy Centre and Aarhus University Hospital, Denmark

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H I G H L I G H T S

- Interrater agreement on seizure termination is high.
- Interrater agreement on the duration of postictal EEG changes is moderate.
- Rater evaluation of postictal duration correlates well with EEG slowing.

A B S T R A C T

Objectives: To compare frequency analysis to human raters and determine the interrater agreement of postictal EEG changes after focal seizures.
Methods: 24 focal seizures with and without impaired awareness recorded with scalp-EEG in the epilepsy monitoring unit were selected. Five board-certified neurophysiologists annotated seizure termination and end of postictal changes for all seizures. We assessed agreement using intraclass correlation, described the band-power changes by time-frequency analysis, and correlated these measures with the rater annotations.
Results: Interrater agreement on the duration of the postictal changes was moderate (0.64, 95% confidence interval: 0.36–0.82). The interrater agreement for seizure termination was excellent (1.00). Median duration of the postictal interval of seizures with impaired awareness was significantly shorter than for seizures with retained awareness ($p = 0.0004$). Mean postictal duration was 16.4 min. Seizure duration did not predict duration of the postictal changes. We found a strong correlation of 0.8 between the median human rater and the duration of the decrease in spectral edge frequency.
Conclusions: The agreement of neurophysiologists is moderate for duration of postictal changes and high for seizure termination. Rater determination of postictal duration is correlated with measures of EEG slowing.
Significance: Disagreement between neurophysiologists on postictal duration need to be considered.
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1. Introduction

Epileptic seizures may elicit behavioral and electroencephalographic changes remitting abruptly at seizure termination or dissipating gradually. This varies widely across seizure types, making unambiguous delineation between ictal and interictal transition difficult. In the case of absence seizures, behavioral responsiveness and EEG return to baseline at seizure termination, but in many cases of focal seizures with impaired awareness, behavioral changes may be present after ictal EEG changes have subsided. Postictal EEG changes may also be present without any apparent effects on behavior or these may be too subtle to be recognized clinically.

Postictal EEG changes occur in 69–81% of focal seizures (So and Blume, 2010) and consist of delta-band slowing in 57–81%, regional attenuation in 29%, and spike activation in 25% (Kaibara and Blume, 1988; So and Blume, 2010). Isolated attenuation without delta activity occurs in only 10% of focal seizures (So and Blume,

* Corresponding author at: Neurophysiology Center, Department of Neurology, Zealand University Hospital, Sygehusvej 10, 4000 Roskilde, Denmark.
E-mail address: icz@regionsjaelland.dk (I.C. Zibrandtsen).

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2010). The variability of duration of the postictal EEG changes was reported in one study to be 275 s (range 7–2450 s) (Kaibara and Blume, 1988).

EEG interpretation is subjective and there is a varying degree of consensus pertaining to different EEG phenomena, e.g. amplitude requirements in sleep scoring, duration, morphology and distribution requirements of spikes and sharp waves. Adherence to consensus guidelines for clinical EEG interpretation can increase interrater agreement (Azuma et al., 2003). It seems plausible that guidelines can improve agreement when the phenomena of interest can be unambiguously described by a limited set of features such as amplitude and duration, unlike postictal changes.

Agreement between EEG interpretation experts can be expressed in terms of interrater statistics either categorically (e.g. seizure vs. non-seizure) or for continuous quantities (e.g. duration of postictal changes). Agreement may vary depending on the type of waveform and the surrounding conditions. Interrater agreement in clinical EEG interpretation is moderate (Benbadis et al., NES Treatment Workshop, 2009; Berg et al., 1992; Dereymaeker et al., 2017).

To our knowledge, interrater agreement has not before been examined for postictal EEG changes after focal seizures. The postictal state describes all behavioral and neuropsychological changes after seizure termination until return to their pre-ictal baseline, which has been reported to last anywhere from hours to days (Rémi and Noachtar, 2010). We focus on the observable EEG changes and refer to these as the postictal interval. Interictal and ictal has been more studied than post-ictal changes. Clarification of the interrater agreement on postictal changes is a necessary step towards determining the features that experts base their decisions upon and this is critical to understand for translation into computer algorithms.

Our aim is to determine the interrater agreement between experienced clinical neurophysiologists evaluating the time of seizure termination and duration of postictal EEG changes after focal seizures. Secondarily, we use a time-frequency analysis to explore band power changes related to the raters' decisions. We also compare postictal duration between seizures with and without impaired awareness.

2. Methods

Focal seizures from patients admitted to the epilepsy monitoring unit (EMU) at Zealand University Hospital between 2015-01-01 and 2017-12-31 were retrospectively identified. Focal to bilateral tonic-clonic seizures were excluded. Seizures within one hour of subsequent sleep intervals were discarded to avoid sleep-related slow waves interfering with the postictal slowing. If repeated seizures occurred within one hour, all the seizures was discarded: The first seizures were discarded because the termination of the postictal interval might be obscured by the subsequent seizures; the following seizures were discarded to avoid intermixing of persisting postictal changes from the previous seizure. Seizures were categorized as aware, unaware or unknown based on behavioral testing as assessed from video recordings, because awareness is an important feature in the classification in focal seizures (Fisher et al., 2017).

All EEG recordings were performed with NicoletOne V5.94 acquisition system using 25 scalp electrodes placed according to the international 10–20 system including inferior temporal chain electrodes. The sampling rate was either 256 or 1024 Hz.

Raters were five board-certified clinical neurophysiologists with 5–30 years of experience in EEG interpretation. They received 24 files for review in Nicolet .e format exported from at least 5 min before seizure onset to approximately 1 h after seizure end. All raters used Nicolet EEG reader for the visual EEG interpretation. They worked apart from each other at different hospitals and did not share information about the ratings. They were all familiar with this software ahead of the study. Raters could digitally change montage and adjust sensitivity and filters as they saw fit, but were not permitted to use frequency analysis tools to prevent disparate rating strategies with some raters focusing much more on automatic frequency estimation than others.

Raters placed an annotation at seizure termination and at end of postictal interval for each file and did so independently. Seizure onset was annotated by the authors (IZ and SW). The annotations were manually read and used to calculate latency from the start of file to seizure termination and end of the postictal interval in seconds. These latencies were used in the rest of the analysis.

2.1. Time-frequency analysis

EEG files were converted to European data format (edf). A preictal resting state baseline with a duration of 2–5 s was defined for all seizures. The edf files were loaded into Matlab version 2018a for further analysis. A complex Morlet wavelet convolution was used to extract power from either T7 or T8 with common average reference depending on seizure onset lateralization. Wavelets were linearly spaced from 0.5 to 12 Hz with 0.25 Hz increments with varying wavelet cycles from 4 to 12. Power was computed across spectra in 1-s bins. Baseline normalization by Z score conversion was used to facilitate a statistical interpretation of power changes. It was computed as the difference between time-frequency results and baseline power divided with the standard deviation of the time-frequency baseline power. Frequency bands were defined as delta (0.5–4 Hz), theta (4–8 Hz) and alpha (8–12 Hz) and the area under the curve (AUC) in the power spectrum was used to represent the power in the respective band and calculated using the Matlab function *trapz*() for approximate integration with the trapezoid method. The spectral edge frequency (SEF) is the frequency that divides the cumulative power spectrum AUC at a given percentage value. We used 50% SEF to represent the spectral shift as time progressed. For visualizations, a moving median filter spanning 30 s was applied to the power data. Noise was conceptualized as the root mean square (rms) of 1-s epochs across each channel. For each EEG record, the mean channel mean rms was compared to the standard deviation of the raters' estimated postictal duration.

2.2. Criterion based determination of the postictal duration

Postictal slowing was conceptualized as a leftward spectral shift summarized by the SEF feature. After median rater seizure termination, we found the first consecutive 10 s of the median filtered SEF time series that was within 2 standard deviations of the preictal SEF baseline. The duration of this interval is the computer rating. We calculated the Pearson's product-moment correlation coefficient between computer rating and each human rater and for computer against the median rating of each seizure.

2.3. Statistics

The latency from seizure termination to the rater's designated end of postictal duration in seconds is a continuous outcome for each seizure by each rater. The inter-rater consistency can be evaluated with the intraclass correlation coefficient in a 2-way random effects model, where the average of the rater value was used as the reference (ICC2k) (Koo and Li, 2016). The assumption is that raters are representatively recruited from the population of experienced raters. Statistics were computed using R (version 3.5.1) using packages psych for function *ICC* and ggplot2 for visualization.

We compared the mean rater duration of the postictal interval between aware and unaware seizures. Levene's test was used to test for unequal variances. A qq-plot of the residuals of an unpaired T-test showed deviations from normality and we instead used Wilcoxon's rank sum test with continuity correction.

Linear regression was used to determine if the duration of the postictal interval increases with seizure duration. In this case, the median rater postictal duration was used to define postictal end. Seizure duration was the duration from seizure onset (not chosen by raters) to the mean of seizure termination annotations by the raters. Models were evaluated by inspection of qq-plots and influence plots of the residuals, hat values and Cook's distances. Influential outliers with Cook's distance > 1 were removed.

3. Results

All 5 raters evaluated 24 seizure from 14 individual patients, 4 male and 10 female, between 13–66 years of age. Of all the seizures, 8 were classified as aware, 13 unaware and 3 were unknown. Of the 24 seizures, 22 were of temporal lobe origin (Table 1). Seizure 5 and 21 were of extratemporal lobe origin, but these propagated to the temporal lobe within a few seconds. Patient 11 had two seizures with different onset zones.

For seizure termination, the ICC estimate is 1.00 (95% CI 1–1), $p < 0.00001$, $F = 749$, which translates to excellent interrater agreement (Koo and Li, 2016) (Fig. 1). We see that the rater seizure termination annotations are superimposed on each other or only marginally displaced. Exceptions are seizure 6, 10 and 11. For seizure 6 and 10, rater 3 is responsible for the deviation away from consensus, whereas the raters are more spread out for seizure 11.

In contrast, there is considerably more variability regarding durations of the postictal intervals (Fig. 2). The ICC estimate for the postictal duration is 0.64 (95% CI 0.36–0.82), $p = 0.000014$, $F = 3.4$. For the majority of seizures the raters differ significantly. For seizure 15 there is more than an hour between rater 3 and the rater 2 and 4. For 7 seizures, at least one rater placed the annotation at the end of file. Seizure 5 and 21 were of extratemporal origin. We re-ran the analysis without these seizures and this did not to change the result (ICC = 0.65 CI 0.36–0.83).

The summary statistics for seizure duration and postictal duration are shown in Tables 2 and 3, respectively. The mean seizure duration ranges from 57.2 to 60.6 s. The raters differ markedly in their assessments of the postictal duration compared to the seizure duration.

Testing the median postictal duration for each seizure excluding the 3 unclassified seizures for a difference between aware and unaware, Wilcoxon's rank sum test showed a significant difference of 164 s (95% CI 31.0 s–770.6 s), $p = 0.0004$. For seizure durations, aware seizure were 23.3 (CI 14.4–31.6) seconds shorter than unaware seizures, $p = 0.00017$.

Do longer seizures also have longer postictal intervals? A linear regression model of postictal duration predicted from seizure duration suggested a significant relationship ($\beta = 0.026$, 95% CI [0.0096, 0.042], $p = 0.0031$, adj. $R^2 = 0.30$). However, when influential outliers were removed, the slope became insignificant ($\beta = 0.006$, 95% CI [0.0037, 0.015], $p = 0.218$, adj. $R^2 = 0.03$) (Supplementary Material S1).

To elucidate the causes of rater disagreement, we inspected the plots of band power changes over time for all seizures (example seizure in Fig. 3, refer to Supplementary Material S2 for all of them). There is a significant delta power increase ictally and it remains elevated compared to the baseline postictally. This represents a leftward spectral shift, described by the lower SEF, which at around 15 min returns to pre-ictal baseline range. This SEF return to baseline is the salient feature captured by the computer rating (green triangle).

At 37 min there is a sudden theta power spike associated with a depression in the SEF, which could appear like the postical change, but at the same time we see highly elevated rms, so we can infer that this is cause by a high frequency artifact. In fact, there was sequential chewing artifacts at this point. Artifacts may be spotted in this manner also for other seizures (see Supplementary Material S2, seizure 9, 11 and 13).

We hypothesized that interrater agreement would be lowered for more noise contaminated EEGs, but a linear regression predicting rater disagreement, expressed as the standard deviation between them for each seizure, from noise conceptualized as the mean channel rms mean was insignificant ($p = 0.8$).

We wanted to compare the human raters with the computer rating and we found a strong correlation of 0.8 between the med-

Table 1
Patient and seizure characteristics.

Seizure number	Patient	Age (yr)	Sex	Seizure Classification	Ictal onset zone	Seizure duration (s)	Abnormal EEG duration (s)
1	1	60	Female	Aware	Left Temporal	41	52
2	1	60	Female	Aware	Left Temporal	39	69
3	1	60	Female	Unaware	Left Temporal	56	628
4	1	60	Female	Unaware	Left Temporal	59	1106
5	2	71	Female	Unaware	Right Frontal	92	103
6	3	29	Male	Unknown	Left Temporal	44	749
7	4	24	Female	Unaware	Right Temporal	18	113
8	4	24	Female	Unknown	Right Temporal	27	37
9	4	24	Female	Aware	Right Temporal	14	24
10	5	46	Female	Unaware	Left Temporal	60	518
11	6	35	Female	Aware	Left Temporal	63	73
12	6	35	Female	Unaware	Left Temporal	155	3375
13	6	35	Female	Unaware	Left Temporal	71	3459
14	7	43	Female	Unaware	Left Temporal	47	748
15	7	43	Female	Unaware	Left Temporal	53	853
16	8	43	Male	Unaware	Left Temporal	37	563
17	9	27	Female	Aware	Left Temporal	79	505
18	9	27	Female	Aware	Left Temporal	65	238
19	10	32	Male	Unknown	Right Temporal	36	1469
20	11	67	Female	Aware	Right Temporal	15	25
21	11	67	Female	Aware	Left Frontal	23	34
22	12	26	Female	Unaware	Right Temporal	248	2866
23	13	56	Male	Unaware	Left Temporal	45	56
24	14	24	Female	Unaware	Left Temporal	49	59

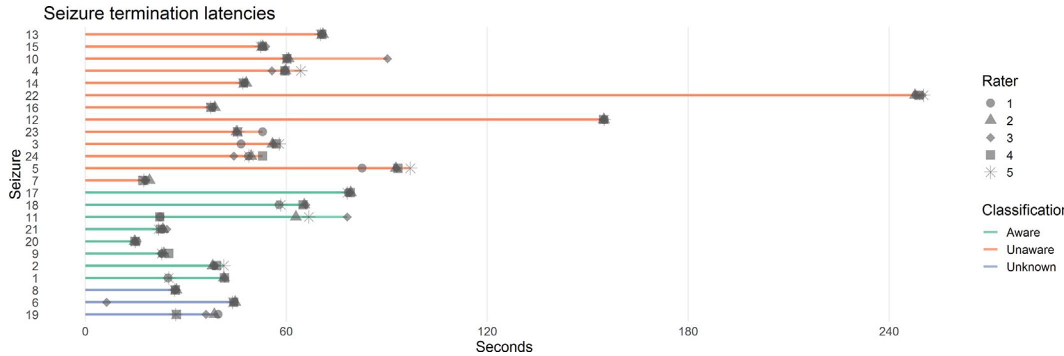

Fig. 1. Latencies from start of file to seizure termination for the different raters. Each rater has a different symbol. Color of the line designate seizure type. Seizures are grouped by classification and sorted within group by ascending standard deviation for rater evaluation of the postical duration. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

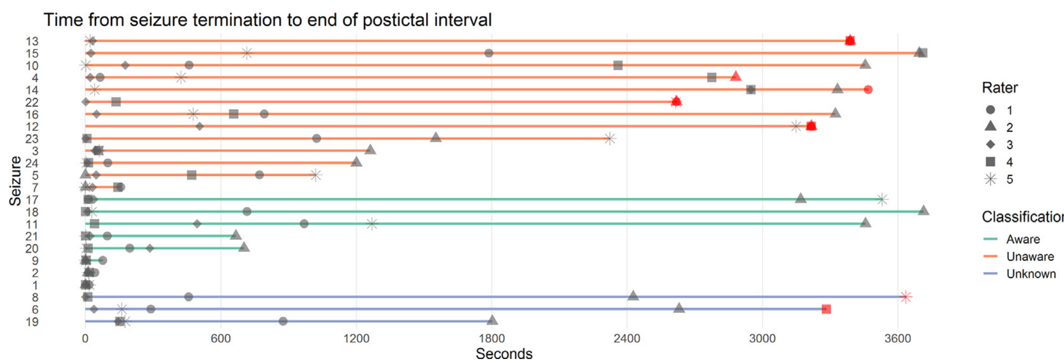

Fig. 2. Latencies from seizure termination to end of the postictal interval by each rater. Each rater has a different symbol. Color of the line designate seizure type. Seizures are grouped by classification and sorted within group by ascending standard deviation for rater evaluation of the postical duration. Rater symbol is red if the annotation was placed at the end of the file. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 2
Summary statistics for seizure durations in seconds.

Rater	Mean	Median	1st IQR	3rd IQR
1	57.2	47.0	26.2	59.7
2	60.6	48.8	38.4	63.4
3	60.4	46.3	33.7	72.4
4	58.5	46.3	27.1	61.4
5	59.6	47.9	26.9	64.9

IQR: Inter-quartile range.

Table 3
Summary statistics for postictal interval durations in seconds.

Rater	Mean	Median	1st IQR	3rd IQR
1	904.5	458.8	92.2	982.8
2	2020.9	2522.7	693.5	3325.3
3	205.5	31.3	9.1	72.8
4	975.9	97.1	11.6	2463.9
5	820.4	111.0	11.8	1082.9

IQR: Inter-quartile range.

ian rater and the SEF-based computer rating (Fig. 4). For the individual raters, the correlation is highest for rater 1 at 0.78 where we see the most clustering near the diagonal. The correlation is lowest for rater 3 at 0.1 with most observations clearly off the diagonal. This may reflect differences in how much weight the raters place upon the SEF shift. When considering the median rating for each seizure, the correlation becomes 0.8, higher than for any individual rater.

4. Discussion

We show a moderate agreement (ICC = 0.64) between expert raters on assessing the duration of postictal changes after focal seizures. However, the confidence interval of 0.36–0.82 means that the agreement between comparable raters evaluating comparable seizure intervals would be somewhere between poor and good. The contrasting excellent interrater agreement (ICC = 1) for seizure duration prompts the question on what lies behind the discrepancy. We hypothesize that the raters put different emphasis on different aspects of the multidimensional changes occurring after seizures. From the time-frequency decomposition we can see that there is almost always a power increase in the delta-theta range representing a left-ward shift in the spectrum. From the correlation analysis we observe that the SEF-based computer rating correlates better for some raters than others (rater 1 compared with rater 3). This indicates that rater 1 puts a stronger emphasis on EEG slowing than rater 3.

For the interrater analysis, we used the intraclass correlation coefficient. This choice has several implications. The random effects ICC model carries an assumption that the raters are randomly recruited from a larger group and then the results are generalizable to the larger population (Koo and Li, 2016). Our raters were invited to participate in the study, but they do in some sense represent sampling from the larger population of neurophysiologists and thus it is reasonable to expect other neurophysiologists to exhibit a similar degree of agreement to what we found.

Instead of establishing agreement on a continuous scale, another choice is to define categories of agreement within certain boundaries, e.g. perfect agreement if two raters are within 5 s of

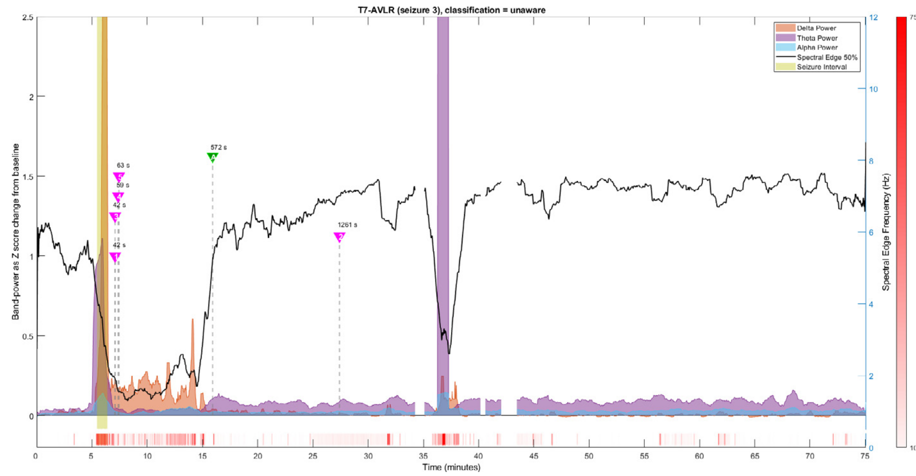

Fig. 3. Baseline-normalized power changes expressed as Z scores for seizure 3, channel T7-Average (left y-axis). Power changes are represented by colored areas. The yellow transparent rectangle represents the seizure interval. The black line is the spectral edge 50% frequency (SEF) (right y-axis). Below the x-axis is color indication of the root mean square (RMS) pr. second. The color bar shows the limits of the color map. Rater annotations of the end of post-ictal changes is marked by magenta triangles. Number of seconds after seizure termination written above. The green triangle is the computer rating for return of SEF to within 2 standard deviation of the pre-ictal mean SEF. Delta power increases significantly during the seizure and remains elevated postictally for 5–10 min compared to the pre-ictal baseline. This is reflected in a SEF decrease during the seizure until approximately the 15 min mark. At around 37 min there is a large power increase coinciding with elevated RMS. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

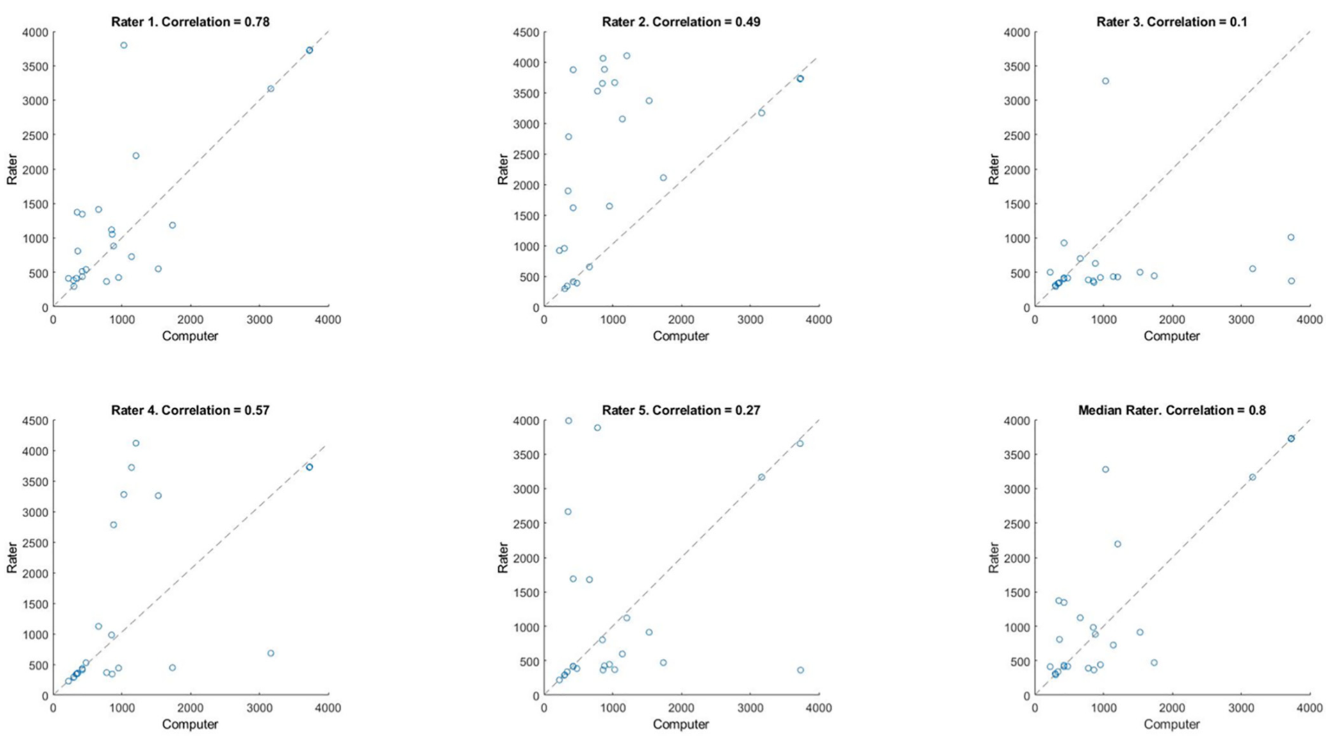

Fig. 4. Correlation between postictal duration (in seconds) for individual raters 1–5 against the computer rating. Bottom-right plot is the median rating for each seizure against the computer ratings.

each other. Such an approach has the advantage that agreement can be expressed in percentages, which facilitates intuitive interpretation. A disadvantage is that the thresholds and categories are necessarily somewhat arbitrary. Since the duration of postictal changes exist on a continuous scale, ICC is an appropriate tool without arbitrary categories and better facilitate comparisons between studies.

We also found that the duration of the postictal interval is significantly longer for seizures with impaired awareness than seizures with unimpaired awareness. This finding is consistent with other studies (Blumenfeld, 2012; Englot et al., 2010) showing that focal seizures with impaired consciousness is associated with a postictal pattern of more slow-wave activity in fronto-parietal networks. In the Supplementary Material (S2), this tendency can be seen for seizure 3, 4, 10, 12, 13, 14, 15, 22 and 23, but not 5, 7 and 16. Some of the plots are difficult to evaluate because of a high noise level, such as for seizure 24.

4.1. Limitations

General recommendations for number of raters and observations is at least 3 and 30, respectively (Koo and Li, 2016). We have less seizure examples than this recommendation, which may contribute to the wide confidence intervals of the postictal duration estimate because of inadequate representation of the heterogeneity in focal seizures and rater assessment, but it is not possible to completely disentangle this from other contributions to disagreement such as noise.

There are 24 seizures from 14 individuals, so some seizures originate from the same patient and because of within-subject seizure similarity this could cause artificially high agreement. We can look to Fig. 2 for signs of bias because, if there is a large effect of within-subject seizure similarity, rater annotations would tend to cluster together within seizures from the same patients. We see no convincing patterns of vertically aligned rater symbols for the seizures from the same individuals.

The majority of the seizures we included were temporal lobe seizures. As such, our findings primarily relate to that particular kind of seizures. Only seizures occurring during wakefulness were selected to disentangle postictal slowing as a pathological phenomenon from natural slowing during sleep. Therefore, our results can only be considered valid for seizures occurring during wakefulness. The level of agreement would be lower in an unselected sample of seizures, as EEG variability would be larger.

More information about the raters would help evaluate the generalizability of our results to other raters. It seems likely that there are national and regional practices on interpretation of certain electroencephalographic features. To overcome this limitation we would have needed raters from several different countries/centres. The raters' level of experience could also be described in more detail (e.g. in terms of number of ictal EEGs evaluated pr. week).

We cannot exclude the possibility that the use of anti-seizure drugs (ASD) during the EEG recordings could have had effects, perhaps especially when patients were tapered out. There is evidence that valproate, lamotrigine and carbamazepine decreases gamma-band activity (Arzy et al., 2010). Barbiturates and benzodiazepines increase beta activity (Duncan, 1987). Gamma- and beta-band was not included in the time-frequency analysis. Carbamazepine reduces the background activity and causes slight increases in theta- and delta power (Besser et al., 1992). These changes occur gradually and we look only at EEG recordings that last approximately 1 h, so tapering of ASDs is unlikely to influence the analysis. However, ASDs might alter the overall postictal electroencephalographic behavior. There is some evidence that levetiracetam reduces the duration of postictal changes (Tilz et al., 2006). Most patients with epilepsy will be on ASDs so restriction of interpretation to that group contains the majority of the population of interest.

The EEG files were generally truncated at approximately 1 h after seizure termination. For several EEGs, one or more raters placed their annotation at the end of the file, indicating that the postictal change may continue beyond this point. This will have the effect of reducing disagreement to some extent. This will also bias the correlation between computer rating and the human raters when SEF does not return to baseline before the end of file, such as in seizure 12, 13 and 22 (Supplementary Material S2). For all files, there were little pre-ictal EEG visible for the raters (Supplementary Material S2) and this may have represented an artificial constraint on the task.

4.2. Perspectives and future research

Considering the disagreement between raters in our study, further studies should have enough raters that differences among rater strategies can be compared to heterogeneity of seizures. This might shed light on differences in judging certain aspects of the EEG more or less important than others. A complementary computerized interpretation of certain features or sets of features may facilitate a data driven approach to the identification of the most robust feature set that best describe EEG transitions corresponding to remission of postictal changes. We used SEF as a single feature to explore this question, but future research should investigate multiple features.

In a clinical context, EEG investigation could be prompted by the desire to obtain lateralizing information after a seizure. Previous studies have pointed to the value of the postictal EEG in lateralizing temporal lobe seizures (Williamson et al., 1993) and frontal lobe seizures (Whitehead et al., 2016). To determine how long after a seizure it such EEG investigation makes sense, a normal range for postictal duration would be informative. This would have required a substantially larger amount of seizures to establish than we had available.

The evaluation of the raters in our study must be expected to be influenced by each individual rater's a priori idea of the duration of postictal intervals; If a rater goes to the task expecting that most postictal changes last 10–20 min, this may bias the estimate in the direction of the pre-conceived presumption. To eliminate this bias, one approach could be removing the time information from the EEG recordings by epoching the recordings and presenting them to the raters in random order, leaving only frequency and waveform morphology for the decision to be based on. Pairing postictal epochs with random pre-ictal baseline epochs, we would expect above chance level separation closer to seizure termination gradually dropping towards chance-levels as postictal changes dissipate. Developing this approach to maturity is outside the scope of our study.

5. Conclusions

Interrater agreement is excellent for seizure termination, but moderate for estimation of postictal duration with indeterminability about true agreement among different sets of raters. The duration of the postictal interval for focal seizures with impaired awareness is significantly longer than focal seizures without impaired awareness, but we did not find that seizure duration predicted postictal duration.

Delta and theta power increased following most seizures causing a left shift in the spectral distribution, and this measure correlates with the median rater. Future studies to determine a set of features to model postictal EEG changes should incorporate features that describe other changes than slowing.

Conflict of interest

No authors have conflicts of interests to declare.

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Author contributions

IZ, SW and TWK were part of the conceptual design of the study. IZ and SW collected and processed the data. SB, MB evaluated and rated the EEGs. IZ did the calculations, statistics and created the figures. IZ and SW drafted the manuscript and TWK, SB and MB revised it. All authors approved the final manuscript before submission.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clinph.2019.03.001.

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