Automatic multimodal detection for long-term seizure documentation in epilepsy

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Abstract

Objective: This study investigated sensitivity and false detection rate of a multimodal automatic seizure detection algorithm and the applicability to reduced electrode montages for long-term seizure documentation in epilepsy patients.

Methods: An automatic seizure detection algorithm based on EEG, EMG, and ECG signals was developed. EEG/ECG recordings of 92 patients from two epilepsy monitoring units including 494 seizures were used to assess detection performance. EMG data were extracted by bandpass filtering of EEG signals. Sensitivity and false detection rate were evaluated for each signal modality and for reduced electrode montages.

Results: All focal seizures evolving to bilateral tonic-clonic (BTCS, n = 50) and 89% of focal seizures (FS, n = 139) were detected. Average sensitivity in temporal lobe epilepsy (TLE) patients was 94% and 74% in extratemporal lobe epilepsy (XTLE) patients. Overall detection sensitivity was 86%. Average false detection rate was 12.8 false detections in 24 h (FD/24 h) for TLE and 22 FD/24 h in XTLE patients. Utilization of 8 frontal and temporal electrodes reduced average sensitivity from 86% to 81%.

Conclusion: Our automatic multimodal seizure detection algorithm shows high sensitivity with full and reduced electrode montages.

Significance: Evaluation of different signal modalities and electrode montages paces the way for semi-automatic seizure documentation systems.

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1. Introduction

Seizure documentation and quantification represents the primary outcome measure of epilepsy therapy including antiepileptic drug treatment, epilepsy surgery, and neurostimulation. Presently, patients document their seizures using seizure diaries without systematic and objective validation approach by physicians. Recent publications showed that manual seizure counting suffers from underreporting with sensitivities of 50% during day and as low as 30% during night and can therefore be considered as highly unreliable (Blachut et al., 2015). This inaccuracy represents a major issue for the assessment of treatment efficacy including drug trials.
We propose a semi-automatic system for seizure documentation and quantification based on computer methods to scan biomedical signals for epileptic seizures followed by a manual evaluation of these detections by trained staff. For this application a low number of sensors should be used to assure patient compliance and to simplify hardware design. On the other hand, data from ictal events needs to be recorded with a reasonable number of sensors to allow post-hoc analysis for correct seizure identification. A prerequisite for this approach is a wearable electrophysiological hardware setup that can be utilized over long time periods. Secondly, and with utterly importance, a clinically validated computer based detection method has to be used. This method has to ensure high sensitivity and low false detection rates, to pay off additional efforts of neurophysiological measurements with numerous EEG electrodes and other sensors.

EEG represents the gold standard in epilepsy diagnosis and to prove the epileptic nature of seizures which makes it the primary modality for automatic seizure documentation. Automatic seizure detection methods based on surface EEG recorded during inpatient epilepsy monitoring showed high sensitivity in multi-center studies (Fürbass et al., 2015a; Hopfgartner et al., 2014). Reduced EEG electrode sets showed a rapid drop in detection sensitivity for rhythmic patterns (Herta et al., 2017) which has to be considered for wearable documentation devices.

ECG can be utilized as another modality for seizure detection. Epileptic seizures cause an activation of the central autonomic network (CAN) resulting in changes in heart rhythm at seizure onset. Ictal tachycardia (ITC) represents the most frequent change in heart rhythm and can be observed in 65–86% of seizures (Eggleston et al., 2014; Leutmezer et al., 2003). Furthermore, a larger affected brain area was reported to define the degree and rate of ITC (Stefanidou et al., 2015). ITC occurs early during seizure evolution and often even precedes EEG changes visible on scalp-EEG (Leutmezer et al., 2003). The high sensitivity of ITC, its early occurrence, and the easy technical setup for ECG measurement makes this biomarker highly promising for automatic seizure detection devices.

Other modalities for automatic seizure detection were investigated recently, including methods based on surface EMG (Beniczky et al., 2016) and motion sensors (Conradsen et al., 2012) as well as gyroscopic sensors and dermal skin conductance sensors (Banks et al., 2014).

In this study we present a multimodal automatic seizure detection method using information from EEG, ECG assessing ictal tachycardia and EMG measuring ictal tonic muscle activity. We investigated this method both with a full 10–20 electrode set as well as a reduced number of EEG electrodes suitable for ambulatory settings. We assessed strengths and weaknesses of this approach in patients with specific seizure and epilepsy types.

2. Methods

2.1. Data

We retrospectively analyzed 92 long-term EEG/ECG/EMG recordings from two epilepsy monitoring units including at least 21 EEG electrodes and at least one ECG channel. Signed informed consent was obtained from all patients. We included all available EEG recordings with one or more epileptic seizure during the recording period resulting in a total of 11,978 h of data with 494 epileptic seizures of various types (min per patient = 23 h, max per patient = 547 h). From 92 patients included in our study 55 patients had temporal lobe epilepsy (TLE) and 37 patients had extratemporal lobe epilepsy (XTLE). Data were recorded with a Micromed (Veneto, SpA) and an Itmed (Natus Medical Incorporated) system at a 256 Hz sampling rate using gold-disc electrodes placed according to the international 10–20 system with additional temporal electrodes. To mimic the behaviour of prospective data, digital EEGs were analyzed without manual pre-processing, data selection or data cutting.

The effect of reduced scalp electrode montages was simulated by removing electrodes from the digital EEG file before further analysis. Two different montages with reduced number of electrodes were assessed: the **8 electrode forehead montage** including electrodes F1, F7, T7, P2, F8, T8, F2, ECG and the **7 electrode posterior montage** including electrodes T7, P7, O1, T8, P8, O2, ECG. Fig. 1 shows standard electrode positions (circles) as well as electrodes of forehead montage (dashed circles) and electrodes of posterior montage (shaded circles).

2.2. Performance evaluation methodology

Seizures were annotated following standard protocols of the two epilepsy monitoring units using both clinical and EEG information. The first three seizures of each patient were categorized according to the ILAE operational seizure classification (http://www.ilae.org/Visitors/Centre/documents/ClassificationSeizureILAE-2016.pdf) in order to facilitate performance evaluation according to seizure type. Seizure markers were set based on standard EMU review procedure using video, EEG, and other clinical information including manual validation of seizures by an experienced clinical epileptologists (HS, SP, or CB). Only validated seizure markers were used to define seizure epochs as basis for assessing detected and undetected seizures. Each seizure epoch ranged from 30 s before the clinical seizure marker to 180 s after this marker resulting in a total 210 s intervals of single seizure epochs.

Our seizure detection algorithm provided both time points and modality of detection. Time points of detected events were compared to the visually identified seizure epochs. Seizure epochs were defined as true positive (TP) if at least one detection occurred within the epoch time range. Detections outside of seizure epochs were defined as false positives (FP). Seizure epochs without a matching detection were defined as false negative (FN). For assessment of detection performance according to seizure types we distinguished between focal seizures (FS group) and focal seizures evolving to bilateral tonic-clonic (BTCS group). The first three seizure epochs including seizure type annotations in each patient were evaluated, consecutive seizure epochs and detections overlapping these epochs were ignored. Patients with at least one seizure of a certain type were included in the corresponding seizure type group. Patients having two different seizure types were included in both seizure type groups.

Sensitivity (SE) was defined as the ratio between the number of true positives (#TP) and the number of all seizures (#TP + #FN) and was calculated for each patient. False detection rate was defined as the number of false detections per 24 h (FD/24 h).

A paired t-test was used as test statistic between performance results of two detector types or electrode sets.

2.3. Computer algorithm

The computer algorithm detects seizures using EEG, surface EMG, and ECG signals that were recorded using scalp EEG and chest ECG electrodes. Fig. 1 gives an overview of the detection system.

EEG is able to pick up pathologic brain activity by showing rhythmic signal components, but patient movements and loose electrode contacts can cause signal artefacts with similar morphology. Before applying the EEG seizure detection algorithm artefacts were removed applying PureEEG, a fully automatic artefact
removal method (Hartmann et al., 2014). A rhythmic pattern detection algorithm described previously (Fürbass et al., 2015b; Herta et al., 2015) was then used to detect rhythmic activity between 1.8 and 12.5 Hz and to measure amplitude and frequency of these patterns. Amplitude baseline was estimated using the 50% percentile of all rhythmic patterns that occurred in the previous four minutes. Rhythmic patterns that were classified as ictal EEG patterns (Fig. 1, (B)) and that had a 40% higher amplitude compared to EEG baseline were defined as seizure detections.

Automatic seizure detection on EMG was based on the occurrence of sustained and excessive EMG activity. EMG signals were extracted from data recorded on EEG electrodes by bandpass filtering the signals between 30 and 60 Hz. Signal strength was quantified using the line length method defined as the sum of distances between each consecutive data sample in non-overlapping 0.5 s windows. Seizure events were defined as high absolute line length values (LL), a steady increase over 5 s, and a 500% increase compared to maximum line length in a four minute baseline window (LL_ref).

ECG signals from a single chest electrode were used for measuring heart rate and for automatic detection of ictal tachycardia. We defined ictal tachycardia as a heart rate above 100 beats per minute (bpm). The detection algorithm first resampled ECG signals to 500 Hz and then high pass filtered the signal with a cut off frequency of 8 Hz to remove T wave components. Then a detection algorithm designed to find periodic patterns scanned for QRS complexes (Fürbass et al., 2015b). The exact time position of R peak was defined at the maximum of the QRS complex. Consecutive R to R time intervals (RR intervals) of the last 10 s were used to define the average bpm at each time point. Cardiac baseline activity was defined as average heart rate during four minutes before the current time point. To differentiate physiologic from ictal activity the modified cardiac sympathetic index based on previous 100 RR intervals (CSI100) was calculated (Jeppesen et al., 2014) as follows: given the Lorenz plot of RR intervals the longitudinal length (L) and the transversal length (T) was estimated as four times the standard deviation. The value of CSI100 was then calculated by $L^2$ divided by $T$. An elevated heart rate of more than 100 bpm
and a minimum increase of 30% compared to baseline as well as a CS100 value above 5 defined a seizure event.

The logical OR combination of the three detection modalities was used for evaluation of the overall system performance. Detection results can be obtained in real time with less than 10% CPU usage of a standard PC; or equivalently a 24 h EEG recording needs approximately 2 h of calculation time. The algorithm will be part of the encevis EEG software package (www.encevis.com).

3. Results

3.1. Detection performance

Assessment of overall detection performance in 92 patients including 494 epileptic seizures resulted in 86% sensitivity (SE) and an average of 16.5 false detections per 24 h (FD/24 h). Evaluation of TLE patients including 284 epileptic seizures resulted in 94% SE and 12.8 FD/24 h. XrLE patients \(n = 37\) including 210 seizures showed a sensitivity of 74% and 22.2 FD/24 h. Evaluation according to seizure types involved a maximum of 3 epileptic seizures per patient (see Section 2.2). The focal seizure (FS) group included 64 patients with 139 seizures and in 89% SE and 16.4 FD/24 h. On the other hand, evaluation of 35 patients with 50 focal seizures evolving to bilateral tonic-clonic seizures (BTCS) resulted in 100% SE and 14.1 FD/24 h.

ECG based seizure detection resulted in low sensitivities (TLE: 40%, XrLE: 8%; FS: 27%, BTCS: 43%). EMG based seizure detection reached high sensitivity for BTCS (93%) but low sensitivities for other patients and seizure types (TLE: 25%, XrLE: 35%; FS: 8%). EEG based seizure detection showed high sensitivities in general (TLE: 91%, XrLE: 74%, FS: 88%, BTCS: 97%).

Electrode set reduction using a 8 electrode forehead montage including frontal and temporal as well as ECG electrodes (FP1, F7, T7, FP2, F8, T8, FZ, ECG) resulted only in statistically non-significant lower detection sensitivity \(p > 0.05\) for XrLE (−6% SE), FS (−5% SE), and BTCS (−3% SE). Significant reduction by −5% was found when all patients and seizures were used (group ALL) with \(p = 0.02\) and for TLE (−6% SE) with \(p = 0.01\).

Reduction to 7 electrode posterior montage including temporal and occipital as well as ECG electrodes (T7, P7, O1, T8, P8, O2, ECG) showed even lower detection sensitivity which was non-significant \(p > 0.05\) only for patients with BTCS (−6% SE), whereas ALL (−12% SE), TLE (−10% SE), XrLE (−15% SE), and FS (−11% SE) showed a significant reduction \(p < 0.05\).

Table 1 summarizes the results separate for different detection modalities (EEG, ECG, EMG), combination of modalities (EEG + EMG, COMB defined as EEG + ECG + EMG) based on data of five different evaluation groups (ALL, TLE, XrLE, FS, BTCS). Detection performance using the full 10–20 electrode set including 21 EEG and 1 ECG electrode (22 electrode montage) as well as the 8 electrode forehead montage and the 7 electrode posterior montage are shown.

Fig. 2 visualizes detection performance by receiver operating characteristic plots (ROC) for full 22 electrode and the 8 electrode forehead montage. The 95% confidence intervals for sensitivity values are shown using vertical error bars of the COMB detector. Comparing COMB performance to EEG + EMG combination shows the added value of an ECG based detection system.

3.2. Detection delays

Time delay of seizure detections are of minor importance to our proposed semi-automatic seizure documentation approach but will be in focus of ambulatory seizure alarming devices. In this section we elaborate on detection delays to get more insights into this closely related and important topic. Comparing time delays of automatically calculated detections to visually selected seizure markers indicated a correlation of average delays with detection modalities. Fig. 3 shows boxplots of detection delays in seconds of all detected seizures based on the full 22 electrode montage. EEG based detections had a median delay of only 19 s (min = −22 s, max = 75 s) followed by EEG based detections (median = 26 s, min = −10 s, max = 165 s), and surface EMG based detections (median = 45 s, min = 6 s, max = 141 s). Negative delays indicate detection of seizures prior to visual identification on scalp-EEG or video, and were found in 16 seizures (ECG = 12, EEG = 4, EMG = 0 seizures). In this work the detection horizon prior to visual

<table>
<thead>
<tr>
<th>Automatic seizure detection performance</th>
<th>22 electrode montage</th>
<th>8 electrode forehead montage</th>
<th>7 electrode posterior montage</th>
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<tr>
<td></td>
<td>SE (%)</td>
<td>FD/24 h</td>
<td>SE (%)</td>
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<tr>
<td>ALL n = 92 nSz = 494</td>
<td></td>
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<tr>
<td>EEG</td>
<td>84</td>
<td>15.6</td>
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<tr>
<td>ECG</td>
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<td>EMG</td>
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<td>0.4</td>
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<tr>
<td>EEG + EMG</td>
<td>84</td>
<td>16.0</td>
<td>92</td>
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<tr>
<td>EEG + ECG + EMG (COMB)</td>
<td>86</td>
<td>16.5</td>
<td>94</td>
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<tr>
<td>TLE n = 37 nSz = 210</td>
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<tr>
<td>EEG</td>
<td>79</td>
<td>11.5</td>
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<td>ECG</td>
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<td>EMG</td>
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<tr>
<td>EEG + EMG</td>
<td>81</td>
<td>12.1</td>
<td>90</td>
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<tr>
<td>EEG + ECG + EMG (COMB)</td>
<td>81</td>
<td>13.5</td>
<td>90</td>
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<td></td>
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<tr>
<td>FS n = 64 nSz = 139</td>
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<tr>
<td>EEG</td>
<td>68</td>
<td>4.2</td>
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<td>EMG</td>
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<td>EEG + EMG</td>
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<tr>
<td>EEG + ECG + EMG (COMB)</td>
<td>74</td>
<td>6.0</td>
<td>84</td>
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</table>
Fig. 2. Detection performance by means of sensitivity and false detections per 24 h (FD/24 h) shown in ROC plots. The left upper corner of each plot defines the theoretical optimum point with 100% sensitivity and no false detections. Results for our seizure algorithm based on different modalities (EEG, EMG, ECG) and their logical OR combination (COMB) are shown. Data of the 22 electrode montage (boxes) and the 8 electrode forehead montage (crosses) is shown. Both montages include the same ECG data wherefore ECG based detection performance results in the same values (box overlaid with cross labelled ECG). Vertical error bars on the COMB values indicate the 95% confidence intervals of sensitivities. All focal seizures evolving to bilateral tonic-clonic (BTCS) are detected with the 22 electrode montage and 97% of BTCS using a reduced forehead montage. The ECG based detector stays below 43% sensitivity in all evaluation groups with false alarm rates below 0.7 FD/24 h.

Fig. 3. Box plots represent time delay of seizure detections for different modalities compared to seizure markers set by clinicians. Whiskers of each box plot include the minimum and maximum value.
identification on scalp-EEG or video was limited to 30 s because of the definition of the seizure epoch (see Section 2.2).

Fig. 3 shows that some detections triggered by the ECG or EEG signal even occurred before clinical onset (whiskers include the minimum and maximum value). Median delays of EEG (19 s), EEG (26 s), and EMG (45 s) detections show that ictal ECG features appear earlier in time compared to EEG based features (although less frequent, see Fig. 2), and that surface EMG has the largest median delay.

4. Discussion

Automatic seizure documentation for outpatients has to proof high sensitivity and needs post-hoc manual evaluation for reliable seizure identification. Low false detection rates are mandatory to reduce workload of manual evaluation procedure. We present a multimodal seizure detection algorithm working in real time that is able to detect epileptic seizures with high sensitivity using EEG, EMG, and ECG signals.

Our results show very high detection sensitivity of 94% for TLE and overall detection sensitivity of 86% using the 22 electrode montage (21 EEG electrodes plus one ECG). Furthermore, the algorithm was able to detect all focal seizures evolving to bilateral tonic-clonic seizures (n = 50). Therefore, our automatic seizure detection system potentially increases sensitivity of seizure documentation compared to manual procedures in all patient and seizure groups.

Reduced electrode montages for automatic seizure documentation assures patient compliance in long-term outpatient settings. For example, omitting posterior electrodes will increase sleep comfort and therefore positively influences EEG quality of nocturnal events. Furthermore, setup time of ambulatory EEG is a major cost factor especially besides data evaluation which is reduced by a factor of three when using 7 EEG electrodes only. We found lower sensitivities compared to the full 10–20 electrode montage (forehead –5% SE, posterior –12% SE). Based on our results we conclude that the 8 electrode forehead montage is most beneficial for this application. Similar montages showed high sensitivities for emergency and prehospital care application (Jakab et al., 2014). Also our previous work using EEG from intensive care unit patients showed promising results of automatic pattern detection based on forehead EEG montages (Herta et al., 2017).

False detection rates of reduced electrode montages dropped down only by ~3 FD/24 h for forehead but by ~10 FD/24 h for posterior montages showing a positive correlation between the number of electrodes and false detection rate that is more pronounced for posterior electrodes.

Results therefore encourage the use of reduced electrode sets based on frontal and temporal electrodes for long-term seizure documentation. Even XTLE patients showing the lowest sensitivity in our study (68% SE), true seizures counts can be significantly improved as compared to manual seizure counting sensitivity of 50% (Blachut et al., 2015).

Reduction of EEG electrodes will negatively influence visual inspection and seizure validation. It is important to limit electrode reduction to maintain interpretability of the EEG. We therefore avoid electrode reduction below 6 EEG electrodes or sole use of non-EEG signals which would not allow seizure validation at all.

We found significantly lower sensitivities for XTLE patients as compared to TLE patients which can be explained by differences in ictal EEG patterns. Visual analysis of false negatives in XTLE showed that these seizures include low amplitude beta, gamma activity, or high amplitude muscle artefacts but only marginal rhythmic activity. The high rate of interictal abnormal EEG activity in these patients is the reason for the high false detection rate of 22 FD/24 h in this evaluation group.

In our study absolute values of EEG based seizure detections were low (TLE: 40%, XTLE: 8%, FS: 27%, BTCS: 43%). These results are in good agreement with previous publications (Eggleston et al., 2014). Discrepancies as compared to other studies (Leutmezer et al., 2003) can be explained by differences in the definition of ictal tachycardia (Eggleston et al., 2014).

Added value of ECG based seizure detection is marginal when full 10–20 EEG is available. Data shows that sensitivity increases by only a few percent or not at all when adding EEG based detections to 21 electrode EEG based detections (TLE: +2%, XTLE: 0%, FS: +1%, SGTC: 0%). Similar results were found for detections based on 8 electrode forehead montage. ECG based detections gain importance only for the less sensitive 7 electrode posterior montage (ALL: +5%, TLE: +7%, XTLE: +1%, FS: +5%, GTCS: 0%). This shows that low sensitive EEG setups can partly recover sensitivity by using other signal modalities like ECG.

EMG signals were extracted from EEG data via a bandpass filter. An important point of this work was to reduce effort of the electro-physiological setup. Furthermore, dedicated EMG signals were not available in the data of this work. Detection sensitivity for focal seizures evolving to bilateral tonic-clonic solely using derived EMG signals was very high (93%) and an additional surface EMG sensor is therefore avoidable. A further advantage of EEG electrode based EMG detection is that recorded EEG data can be used to validate the EMG based seizure alarms which is impossible with accelerometer data alone.

Accelerometer sensors are able to detect clonic or tonic-clonic seizures with high sensitivity. Detection performance of 66% sensitivity and 1.1 false detections per night was reached (Van de Vel et al., 2016). Combination of accelerometer data and dermoelectrical activity (EDA) reached 89% sensitivity and 93% specificity on data of 8 patients (Heldberg et al., 2015). In this work EMG based seizure detections reached 93% for SGTC and showed a shorter detection delay than accelerometer based detectors.

Comparing detection performance of the presented multimodal seizure detection algorithm to the online seizure detection method EpiScan (Fürbass et al., 2015a) shows that a higher sensitivity for TLE (94–83%) and XTLE patients (74–64%) but also a higher false detection rate (TLE 12.8–6.7, XTLE: 22.2–7.3 FD/24 h) can be reached. On the other hand comparing results of our study to results of a study published by Hopfengärtnert et al. (2014) shows higher sensitivity for TLE (94–89%) but lower sensitivity for XTLE (74–77%). False alarm rate reported in (Hopfengärtnert et al., 2014) is lower compared to results of our study (12.8–4.5 FD/24 h). The higher sensitivity of the multimodal seizure detection algorithm and low CPU calculation time fit the use case of semi-automatic seizure documentation. In turn, the very low false alarm rate of EpiScan and similar algorithms is well suited for triggering acoustic alarms for patient surveillance.

In this work we presented an automatic seizure detection algorithm and results of retrospective data analysis. We are fully aware that a complete seizure documentation infrastructure has to include wearable electrode systems for monitoring, storing detected seizure periods, and IT infrastructure as well as software for transmitting and reviewing stored seizure data for final validation.

5. Conclusion

We presented an automatic multimodal seizure detection algorithm for long-term seizure documentation. Evaluation of detection performance on 92 long-term EEG/ECG/EMG recordings from two epilepsy monitoring units including 11,978 h of data and 494 seizures resulted in high detection sensitivity. The effect of different signal modalities on detection performance and detection
delay was analyzed in detail. The effect of reduced electrode montages on detection performance showed the superiority of frontal and temporal EEG electrodes for automatic seizure detection. The work showed that improved long-term seizure documentation is possible using automatic seizure detection algorithms based on only 8 frontal and temporal as well as one ECG electrode. We conclude that using semi-automatic seizure documentation will improve seizure documentation in general and justifies the additional electrophysiological effort.

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Conflict of interest: The authors declare that they have no conflicts of interest concerning this article.

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