Published in final edited form as:

J Neurosci Methods. 2012 November 15; 211(2): 265–271. doi:10.1016/j.jneumeth.2012.09.003.

A comparison between automated detection methods of high-frequency oscillations (80–500 Hz) during seizures

Pariya Salami^a, Maxime Lévesque^a, Jean Gotman^a, and Massimo Avoli^{a,b,*}^aMontreal Neurological Institute and Department of Neurology & Neurosurgery, McGill University, Montréal, H3A 2B4 QC, Canada^bDepartment of Experimental Medicine, Faculty of Medicine & Odontology, Sapienza Università di Roma, 00185 Rome, Italy

Abstract

High-frequency oscillations (HFOs, ripples: 80–200 Hz, fast ripples: 250–500 Hz) recorded from the epileptic brain are thought to reflect abnormal network-driven activity. They are also better markers of seizure onset zones compared to interictal spikes. There is thus an increasing number of studies analysing HFOs in vitro, in vivo and in the EEG of human patients with refractory epilepsy. However, most of these studies have focused on HFOs during interictal events or at seizure onset, and few have analysed HFOs during seizures. In this study, we are comparing three different automated methods of HFO detection to two methods of visual analysis, during the pre-ictal, ictal and post-ictal periods on multiple channels using the rat pilocarpine model of temporal lobe epilepsy. The first method (method 1) detected HFOs using the average of the normalised period, the second (method 2) detected HFOs using the average of the normalised period in 1 s windows and the third (method 3) detected HFOs using the average of a reference period before seizure onset. Overall, methods 2 and 3 showed higher sensitivity compared to method 1. When dividing the analysed traces in pre-, ictal and post-ictal periods, method 3 showed the highest sensitivity during the ictal period compared to method 1, while method 2 was not significantly different from method 1. These findings suggest that method 3 could be used for automated and reliable detection of HFOs on large data sets containing multiple channels during the ictal period.

Keywords

High frequency oscillation; Automated detection; Analysis; Epilepsy; Seizure

1. Introduction

High-frequency oscillations (HFOs, ripples: 80–200 Hz, fast ripples: 250–500 Hz) have been recorded in experimental epilepsy models and in patients with refractory epilepsy (Engel and da Silva, 2012; Jefferys et al., 2012). HFOs are thought to reflect abnormal network-driven

*Corresponding author at: Montreal Neurological Institute, 3801 University Street, Montréal, H3A 2B4 PQ, Canada. Tel.: +1 514 998 6790; fax: +1 514 398 8106. massimo.avoli@mcgill.ca (M. Avoli).

Conflicts of interest statement

None of the authors has any conflict of interest to disclose.

activity and may help to locate seizure onset zones (Jacobs et al., 2008, 2009; Crépon et al., 2010; Lévesque et al., 2011).

Using automated algorithms to detect HFOs is preferable, since using visual analysis is time consuming and requires experienced reviewers. Moreover, one needs to consider inter-rater reliability and come to an agreement between reviewers on what has to be considered as HFOs (Gardner et al., 2006; Zelman et al., 2012). Thus, multiple automated methods of HFO detection have been developed in recent years. However, most of these studies focused on the detection of HFOs during interictal periods (Staba et al., 2002; Bragin et al., 2004; Jacobs et al., 2009; Lévesque et al., 2011). Few studies have explored HFOs during seizures. In this paper, we are comparing three automated methods to detect HFOs during the pre-ictal, ictal and post-ictal periods of seizures in the rat pilocarpine model of temporal lobe epilepsy. We report here that an automated method that uses a reference period before seizure onset for signal normalisation produces results that are similar to what is detected with visual analysis.

2. Materials and methods

2.1. Animal preparation

Sprague–Dawley rats (250–300 g) were injected with scopolamine methylnitrate (1 mg/kg, i.p.; Sigma–Aldrich, Canada) and 30 min later with a single dose of pilocarpine hydrochloride (380 mg/kg, i.p.; Sigma–Aldrich, Canada) (Bortel et al., 2010; Lévesque et al., 2011). Their behaviour was scored according to the Racine scale (Racine, 1972), and *status epilepticus* (SE) was defined as continuous stage 5 seizures. *Status epilepticus* was terminated after 1 h by injection of diazepam (5 mg/kg, i.p.; CDMV, Canada) and ketamine (50 mg/kg, i.p.; CDMV, Canada) (Martin and Kapur, 2008). The mortality rate was 13%. Surviving animals were allowed to recover for 72 h before surgery. Four stainless steel screws (2.4 mm length) were fixed to the skull and 4 small holes were drilled to allow the implantation of bipolar electrodes (20–30 k Ω ; 30–50 mm length; distance between exposed tips: 500 μ m) made by twisting and glueing two 0.1524 mm resin-insulated copper wires. Contacts consisted of the cut edge of the wire (0.018 mm²) (Châtillon et al., 2011). Electrodes were implanted in the CA3 subfield of the ventral hippocampus (AP: –4.4, ML: $\pm$ 4, DV: –8.8), medial entorhinal cortex (AP: –6.6, ML: $\pm$ 4, DV: –8.8), ventral subiculum (AP: –6.8, ML: $\pm$ 4, DV: –6) and dentate gyrus (AP: –4.4, ML: $\pm$ 2.4, DV: 3.4). Screws and electrode pins were connected with a pin connector and fastened to the skull with dental cement. A cortical screw placed in the frontal bone was used as reference, and a second screw, placed on the opposite side of the frontal region, was used as ground (for more details see: Lévesque et al., 2011).

2.2. Local field potential recordings

After surgery, rats were housed individually in custom-made Plexiglas boxes (30 cm $\times$ 30 cm $\times$ 40 cm) and let habituate to the environment for 24 h. The pin connector was then connected to a multichannel cable and electrical swivel (Slip ring T13EEG, Air Precision, France; or Commutator SL 18C, HRS Scientific, Canada) and LFP-video monitoring (24 h per day) was performed. LFPs were amplified via an interface kit (Mobile 36ch LTM

ProAmp, Stellate, Montreal, QC, Canada), low-pass filtered at 500 Hz and sampled at 2 kHz per channel. Infrared cameras were used to record day/night video files that were time-stamped for integration with the electrophysiological data using monitoring software (Harmonie, Stellate, Montreal, QC, Canada). Throughout the recordings, animals were placed under controlled conditions (22 ± 2 °C, 12 h light/dark schedule) and provided with food and water ad libitum. LFP-video recordings were performed up to 15 days after *status epilepticus*.

2.3. Selection of samples for HFO analysis

Only seizures with good quality signals were selected for analysis. A total of 43 seizures ($n = 6$ animals) were thus extracted during the chronic period, on average $5.5 (\pm 2.3)$ days after SE. These periods were then exported to Matlab 7.9.0 (Mathworks, Natick, MA) using custom-built routines, and analysed off-line.

Seizures were analysed from 60 s before the onset until 50 s after the end of the seizure. Then, 1 s sample traces from each seizure were randomly selected from one of the 4 regions recorded ($n = 100$, 25 traces from each region). Of the 100 selected traces, 43% were extracted from the pre-ictal period, 44% from the ictal period and 13% from the post-ictal period. Every 1 s trace was analysed using 2 methods of visual analysis and 3 automated methods, as described in the following sections (see Sections 2.5 and 2.6).

2.4. Filtering of signals

Raw LFP recordings were band-pass filtered in the 80–200 Hz and in the 250–500 Hz frequency range using an FIR filter; zero-phase digital filtering was used to avoid phase distortion. Fig. 1 shows a seizure from the CA3 region of hippocampus with the filtered signals in the ripple (80–200 Hz) and fast ripple frequency band (250–500 Hz). Every automated method employed a multi-parametric algorithm using routines based on standardised functions in Matlab 7.9.0.

2.5. Visual analyses of HFOs

For the first method of visual analysis, four reviewers trained in electrophysiology and HFO analysis marked events in every 1 s selected traces ($n = 100$). Reviewers were provided with the raw LFP signal (1 s in duration) as well as the filtered signals in the ripple (80–200 Hz) and fast ripple (250–500 Hz) frequency band. Reviewers were asked to mark oscillations as HFOs if they could clearly see oscillations having 3 consecutive cycles with amplitude higher than the average of the background. Every event detected by at least 3 reviewers was then considered as HFOs and the remaining oscillations were excluded from the analysis. Fig. 2D shows oscillations detected by at least 3 of 4 reviewers in one sample trace. The parameters of this visual analysis were similar to the parameters used by the automated method 2 (see Section 2.6.2).

Four different reviewers identified HFOs using the second method of visual analysis. They were provided with a 10 s filtered time-reference trace and with a 1 s filtered trace in each frequency band (ripples and fast ripples). The 10 s time-reference trace corresponded to a period ranging from 50 s to 40 s before seizure onset. Reviewers were asked to identify

oscillations as HFOs if they could clearly see oscillations having 3 consecutive cycles higher than the average of the reference period. Again, HFOs detected by at least 3 reviewers were included in the analysis and the remaining detected oscillations were excluded from the study. The parameters of this visual analysis were similar to the parameters used by the automated method 3 (see Section 2.6.3).

2.6. Automated methods

2.6.1. Automated method 1—The first method used to detect HFOs was built to be similar to what is used to detect HFOs during interictal periods (Staba et al., 2002; Bragin et al., 2004; Lévesque et al., 2011). The filtered traces in each frequency band are normalised using their own average and standard deviation. Thus, for each channel the average of the filtered signal, from 60 s before the start of the seizure to 50 s after the end of the seizure, was computed. Then, the signal was normalised according to the average so that the normalised signal had an average (Avg) of 0 and standard deviation (SD) of 1.

$$\text{Normalised LFP} = \frac{\text{Raw(LFP)} - \text{Avg(LFP)}}{\text{SD(LFP)}}$$

HFOs had to show more than three consecutive cycles (Bragin et al., 2004; Lévesque et al., 2011) higher than a standard threshold (3 SD above the background mean). Moreover, the time lag between two consecutive cycles in the ripple frequency range had to be between 5 and 12.5 ms for ripples, and between 2 and 4 ms for fast ripples. Fig. 2A shows a sample trace with HFOs detected by method 1.

2.6.2. Automated method 2—The selected traces of every seizure were first divided in 1 s trace. Every 1 trace was then normalised using its own root mean square (RMS), where:

$$\text{Normalised 1 s LFP sample} = \frac{\text{Raw(1 s LFP sample)}}{\text{RMS(1 s LFP sample)}}$$

After having normalised traces for each frequency band, oscillations with 3 consecutive cycles having an amplitude above 4 SD of the background mean were detected. As in method 1, the time lag between two consecutive cycles in the ripple frequency range had to be between 5 and 12.5 ms for ripples, and between 2 and 4 ms for fast ripples. Fig. 2B shows a sample trace with the detected oscillations using method 2.

2.6.3. Automated method 3—The third method detected HFOs in each frequency band according to a reference period. A 10 s artefact-free period (50–40 s before the start of the seizure) was selected as a reference period for signal normalisation. LFP in the pre-ictal, ictal and post-ictal periods were normalised using the average and SD of the reference.

$$\text{Normalised LFP} = \frac{\text{Raw(LFP)} - \text{Avg(Ref)}}{\text{SD(Ref)}}$$

Oscillatory events in each frequency band were considered as HFOs if they showed at least three consecutive cycles above a standard threshold (3 SDs above the mean of the reference) (Bragin et al., 2004; Lévesque et al., 2011). Again, as in method 1, the time lag between two consecutive cycles in the ripple frequency range had to be between 5 and 12.5 ms for ripples, and between 2 and 4 ms for fast ripples. Fig. 2C shows a sample trace with the detected oscillations by method 3.

2.7. Statistical analysis

2.7.1. Sensitivity—We first compared the sensitivity of all three methods. We thus calculated in each sample trace ($n = 100$) the number of “true positives”, defined as HFOs detected by each of the automated methods and one of the visual analyses. Thus, the sensitivity of each automated method was defined as:

$$\frac{\text{Number of true positives}}{\text{Number of true positives} + \text{Number of false negatives}} \times 100$$

Since values were not normally distributed, the average sensitivity of the three methods was compared using non-parametric Friedman tests followed by post hoc tests to which a Bonferroni correction for multiple comparisons was applied. The comparison of the average sensitivity during the pre-ictal, ictal and post-ictal periods was compared using non-parametric Kruskal–Wallis tests followed by Bonferroni post hoc corrections for multiple comparisons. The level of significance was set at $p < 0.05$.

2.7.2. False detections—We then compared the number of “false detections” defined as HFOs detected by an automated method that was not detected by any of the reviewers. For each 1 s trace, the number of “false detections” was calculated and then divided by the total number of detected oscillations. The average number of “false detections” during the entire trace was compared using non-parametric Kruskal–Wallis tests followed by Bonferroni post hoc tests for multiple comparisons.

3. Results

Method 1 detected 14 ripples and 25 fast ripples in the 100 sample traces. Method 2 detected 51 ripples and 80 fast ripples. Method 3 detected 156 ripples and 125 fast ripples. Reviewers that used the first visual analysis detected a total of 671 HFOs, 90 of which were detected by all 4 reviewers, 117 by 3 reviewers, 165 by 2 reviewers and 299 by only one reviewer. On the other hand, reviewers that used the second visual analysis detected a total of 1173 HFOs, among which 195 were detected by 4 reviewers, 202 by 3 reviewers, 279 by 2 reviewers and 503 by only one reviewer. Table 1 shows a summary of the number of detected oscillations.

3.1. Comparison of the overall sensitivity between automated methods calculated with results obtained from the first visual analysis

As mentioned earlier, the HFOs that were detected by both the automated method and the visual analysis were considered as “true” HFOs. A total of 11 true positives in the ripple frequency range and 21 true positives in the fast ripple frequency range were detected by

method 1. Method 2 detected 37 true ripples and 60 true fast ripples. Method 3 detected 57 true ripples and 58 true fast ripples. Fig. 3A shows the sensitivity of each method for ripples and fast ripples.

We observed a significant effect of method when comparing sensitivity levels ($X^2 = 44.7$, $df = 5$, $p < 0.001$). As it can be seen in Fig. 3, for ripples and fast ripples, post hoc tests showed that the sensitivities of methods 2 and 3 were higher compared to the sensitivity of method 1 ($p < 0.05$). No significant differences were observed when comparing methods 2 and 3.

Overall, these results suggest that the sensitivity levels of methods 2 and 3 are similar to the first visual analysis for detecting both ripples and fast ripples. Method 1 that is normally used for the analysis of HFOs during the interictal periods performs poorly in terms of sensitivity compared to methods 2 and 3.

3.2. Comparison between the sensitivities of the automated methods and the first visual analysis for the pre-ictal, ictal and post-ictal periods

3.2.1. Pre-ictal period—During the pre-ictal period, method 1 detected 3 true ripples and 11 true fast ripples. Method 2 detected 16 true ripples and 22 true fast ripples. Method 3 detected 18 true ripples and 17 true fast ripples. There was a significant effect of method ($X^2 = 11.5$, $df = 5$, $p < 0.05$) but post hoc comparisons revealed no significant differences between them (Fig. 3B).

3.2.2. Ictal period—During the ictal period, method 1 detected 8 true ripples and 10 true fast ripples. Method 2 detected 17 true ripples and 31 true fast ripples. Method 3 detected 32 true ripples and 33 true fast ripples. There was a significant effect of method ($X^2 = 18.1$, $df = 5$, $p < 0.005$) and post hoc comparisons showed that the sensitivity of method 3 for ripples is significantly higher compared to method 1 ($p < 0.05$) (Fig. 3C). No significant differences were observed between methods for fast ripples.

3.2.3. Post-ictal period—No true ripples or true fast ripples were detected by method 1. Method 2 detected 4 true ripples and 7 true fast ripples. Method 3 detected 7 true ripples and 8 true fast ripples. We observed no significant effect of methods. Overall, these results suggest that when using automated methods of HFO detection in different periods (pre-ictal, ictal and post-ictal), the sensitivity of method 3 is higher compared to method 1, but only during the ictal period and only for ripples. Method 2 does not perform better than method 1.

3.3. Comparison of the overall sensitivity between automated methods calculated with results obtained from the second visual analysis

As in the previous section, we first compared the sensitivity of the automated methods by calculating their overall sensitivity, obtained by comparing detected HFOs with those obtained from the second visual analysis. Results showed that method 1 detected 13 true ripples and 21 true fast ripples. Method 2 detected 41 true ripples and 61 true fast ripples. Method 3 detected 97 true ripples and 85 true fast ripples. Statistical analyses showed a significant effect of method ($X^2 = 61.4$, $df = 5$, $p < 0.05$). Post hoc comparisons showed that

the sensitivities of methods 2 and 3 were significantly higher compared to method 1 ($p < 0.05$) (Fig. 4A).

Overall, these results suggest that methods 2 and 3 have higher sensitivity compared to method 1 in detecting both ripples and fast ripples, when the second method of visual analysis is used as the gold standard.

3.4. Comparison between the sensitivities of the automated methods and the second visual analysis for the pre-ictal, ictal and post-ictal periods

3.4.1. Pre-ictal period—Method 1, detected 4 true ripples and 12 true fast ripples. Method 2 detected 15 true ripples and 21 true fast ripples and method 3 detected 20 true ripples and 21 true fast ripples. Although we observed a significant effect of methods ($X^2 = 11.7$, $df = 5$, $p < 0.05$), there was no significant difference between them (Fig. 4B).

3.4.2. Ictal period—Method 1 detected 9 true ripples and 9 true fast ripples. Method 2 detected 21 true ripples and 33 true fast ripples, and method 3 was able to detect 70 true ripples and 54 true fast ripples. Statistical analysis showed a significant effect of method ($X^2 = 37.5$, $df = 5$, $p < 0.05$) and post hoc tests showed a significant difference between the sensitivity of methods 1 and 3 ($p < 0.05$), for both ripples and fast ripples (Fig. 4C).

3.4.3. Post-ictal period—No true ripples or true fast ripples were detected by method 1. Method 2 detected 5 true ripples and 7 true fast ripples, whereas method 3 detected 7 true ripples and 10 true fast ripples. No significant difference was observed between methods (Fig. 4D).

These results suggest that when dividing seizures into the pre-ictal, ictal and post-ictal periods, we observed that method 3 has higher sensitivity compared to method 1, but only for the ictal period. No significant differences were observed between the sensitivities of the three automated methods for the pre- and post-ictal periods.

3.5. False detection of HFOs

3.5.1. Comparisons with the first visual analysis—When comparing results obtained with the automated methods to results obtained with the first visual analysis, method 1 detected 2 “false” ripples and 2 “false” fast ripples. Method 2 detected 3 “false” ripples and 4 “false” fast ripples. Method 3 detected 58 “false” ripples and 38 “false” fast ripples. Statistical analysis showed a significant effect of methods ($X^2 = 35.8$, $df = 5$, $p < 0.001$) and post hoc tests showed that method 3 is detecting significantly more “false” ripples compared to methods 2 and 1, whereas no significant differences were observed between methods for fast ripples (Fig. 5A). The high number of “false” ripples associated to method 3 was also higher during the ictal discharge (data not shown). This high number of false positives associated to method 3 could however be caused by the low number of detected events associated to the first method of visual analysis, since this difference is not observed when using the second method of visual analysis (see next section).

3.5.2. Comparisons with the second visual analysis—In contrast, when comparing results obtained with those obtained with the second visual analysis, method 1 detected no

“false” ripple and 1 “false” fast ripple, method 2 detected 5 “false” ripples and 4 “false” fast ripples, and method 3 detected 17 “false” ripples and 4 “false” fast ripples. We observed a significant effect of methods ($X^2 = 35.8$, $df = 5$, $p < 0.001$) but no significant differences between them for both ripples and fast ripples. Thus, when comparing “false” HFOs detected with those obtained with the second visual analysis, the number of false detections is similar between methods (Fig. 5B).

4. Discussion

The main findings of our study can be summarised as follows: (1) when grouping all the periods (pre-ictal, ictal and post-ictal), method 3 shows higher sensitivity compared to method 1, when the first and second methods of visual analyses are used as gold standards for the detection of HFOs; (2) when performing separate analyses for each period, method 3 shows higher sensitivity compared to method 1 during the ictal period; (3) the false detection rate of method 3 for ripples is significantly higher than methods 1 and 2 when the first visual analysis is used as the gold standard, but performs equally to the other two methods for fast ripples and when the second method of visual analysis is used as the gold standard. Therefore, we suggest that by using a reference period before seizure onset for signal normalisation, as used in method 3, it produces results that are more similar to both methods of visual analysis when detecting HFOs during seizures.

One of the main advantages of using method 3 is that it can be easily implemented in any software, and parameters can be modified and adapted according to the type of signal that is analysed. The time-consuming visual analysis that is usually performed on EEG traces would thus be greatly reduced since only a fast inspection of suspicious HFO events could be performed. For instance, HFOs caused by movement artefacts or those associated to sharp transients would have to be removed. However, by adding new parameters such as the wavelet transforms (Crépon et al., 2010) or by computing the time-frequency spectrum of each detected event (Bénar et al., 2010), one could identify events for which the energy of the oscillations spreads over the entire spectrum, and that are often caused by sharp transients.

Finally, it remains to be known whether this method can be applied to other types of signal, such as the cortical EEG or the depth recordings from epileptic patients. We have however shown recently that it can be applied to in vitro signals, since HFOs were detected during ictal events recorded in slices from the piriform cortex (Panuccio et al., 2012). Further studies should also investigate whether this method can be applied to HFO detection during interictal periods. There would however be a need to select an artefact-free reference period between interictal spikes.

In conclusion, to our knowledge, this is the first method of HFO detection that can be applied to both the pre-, ictal and post-ictal periods. From a clinical perspective, analysing HFOs during seizures could reveal the underlying mechanisms of seizures and help to develop targeted therapeutic interventions in epileptic patients.

Acknowledgments

This study was supported by the Canadian Institutes of Health Research (CIHR grants 8109, 74609 and 102710).

References

- Bénar CG, Chauvière L, Bartolomei F, Wendling F. Pitfalls of high-pass filtering for detecting epileptic oscillations: a technical note on false ripples. *Clin Neurophysiol.* 2010; 121:301–10. [PubMed: 19955019]
- Bortel A, Lévesque M, Biagini G, Gotman J, Avoli M. Convulsive status epilepticus duration as determinant for epileptogenesis and interictal discharge generation in the rat limbic system. *Neurobiol Dis.* 2010; 40:478–89. [PubMed: 20682341]
- Bragin A, Wilson CL, Almajano J, Mody I, Engel J. High-frequency oscillations after status epilepticus: epileptogenesis and seizure genesis. *Epilepsia.* 2004; 45:1017–23. [PubMed: 15329064]
- Châtillon CE, Zemann R, Bortel A, Avoli M, Gotman J. Contact size does not affect high frequency oscillation detection in intracerebral EEG recordings in a rat epilepsy model. *Clin Neurophysiol.* 2011; 122:1701–5. [PubMed: 21429792]
- Crépon B, Navarro V, Hasboun D, Clemenceau S, Martinerie J, Baulac M, et al. Mapping interictal oscillations greater than 200 Hz recorded with intracranial macroelectrodes in human epilepsy. *Brain.* 2010; 133:33–45. [PubMed: 19920064]
- Engel, J., da Silva, FL. High-frequency oscillations – where are we and where we need to go. *Prog Neurobiol.* 2012. <http://dx.doi.org/10.1016/j.pneurobio.2012.02.001>
- Gardner AB, Worrel GA, Marsh E, Dlugos D, Litt B. Human and automated detection of high-frequency oscillations in clinical intracranial EEG recordings. *Clin Neurophysiol.* 2006; 118:1134–43.
- Jacobs J, LeVan P, Chander R, Hall J, Dubeau F, Gotman J. Interictal high-frequency oscillations (80–500 Hz) are an indicator of seizure onset areas independent of spikes in the human epileptic brain. *Epilepsia.* 2008; 49:1893–907. [PubMed: 18479382]
- Jacobs J, LeVan P, Châtillon CE, Olivier A, Dubeau F, Gotman J. High frequency oscillations in intracranial EEGs mark epileptogenicity rather than lesion type. *Brain.* 2009; 132:1022–37. [PubMed: 19297507]
- Jefferys, JG., Menendez de la Prida, L., Wendling, F., Bragin, A., Avoli, M., Timofeev, I., et al. Mechanisms of physiological and epileptic HFO generation. *Prog Neurobiol.* 2012. <http://dx.doi.org/10.1016/j.pneurobio.2012.02.005>
- Lévesque M, Bortel A, Gotman J, Avoli M. High-frequency oscillations (80–500 Hz) and epileptogenesis in temporal lobe epilepsy. *Neurobiol Dis.* 2011; 42:231–41. [PubMed: 21238589]
- Martin BS, Kapur J. A combination of ketamine and diazepam synergistically controls refractory status epilepticus induced by cholinergic stimulation. *Epilepsia.* 2008; 49:248–55. [PubMed: 17941842]
- Panuccio G, Sanchez G, Lévesque M, Salami P, de Curtis M, Avoli M. On the ictogenic properties of the piriform cortex in vitro. *Epilepsia.* 2012; 53:459–68. [PubMed: 22372627]
- Racine RJ. Modification of seizure activity by electrical stimulation. II. Motor seizure. *Electroencephalogr Clin Neurophysiol.* 1972; 32:281–94. [PubMed: 4110397]
- Staba RJ, Wilson CL, Bragin A, Fried I, Engel J. Quantitative analysis of high-frequency oscillations (80–500 Hz) recorded in human epileptic hippocampus and entorhinal cortex. *J Neurophysiol.* 2002; 88:1743–52. [PubMed: 12364503]
- Zemann R, Mari F, Jacobs J, Zijlmans M, Dubeau F, Gotman J. A comparison between detectors of high frequency oscillations. *Clin Neurophysiol.* 2012; 123:106–16. [PubMed: 21763191]

HIGHLIGHTS

- We compared three automated methods of HFOs detection with two methods of visual analysis during seizures.
- The methods showed similar levels of sensitivity during pre-ictal and post-ictal periods.
- Method 3 showed a higher sensitivity compared to method 1 during the ictal period.
- All methods performed equally in terms of false detection when comparing with the second visual analysis.

Fig. 1.

Representative local field potential recordings showing a seizure (* is indicating the onset and + is indicating the end of the seizure) from the CA3 region of hippocampus in a single rat. Filtered traces in the ripple (80–200 Hz) and fast ripple frequency bands (250–500 Hz) are shown.

Fig. 2.

(A) sample trace from the seizure shown in Fig. 1. Red asterisks indicate the detected ripples and fast ripples by three automated methods (method 1 (A), method 2 (B) and method 3 (C)). (D) Ripples and fast ripples (rectangles) detected with the visual analysis. The filtered trace in the fast ripple frequency range was split in half to facilitate the detection of oscillations. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

Fig. 3.

(A) Overall sensitivity of the three automated methods according to the first visual analysis. The sensitivity (Number of true positives/(Number of true positives + Number of false negatives)) $\times 100$ of methods 2 and 3 were significantly higher compared to method 1 for both ripples and fast ripples. Sensitivity of the automated methods during the pre-ictal period (B), the ictal period (C) and the post-ictal period (D). The sensitivity of method 3 was significantly higher compared to method 1, but only for ripples ($*p < 0.05$).

Fig. 4.

(A) Overall sensitivity of each automated methods according to the second visual analysis. The sensitivity (Number of true positives/(Number of true positives + Number of false negatives)) $\times$ 100 of methods 2 and 3 were significantly higher compared to method 1 for both ripples and fast ripples. Sensitivity of the automated methods during the pre-ictal period (B), the ictal period (C) and the post-ictal period (D). Method 3 showed higher sensitivity compared to method 1 for both ripples and fast ripples.

Fig. 5.

(A) The percentage of false detections of each of the automated methods according to the first visual analysis. Method 3 showed higher false detection but only for ripples and when the first visual analysis was used as the gold standard. (B) The percentage of false detections of each of the automated methods according to the second visual analysis. No significant differences between methods were observed.

Table 1

Number of detected oscillation by each method.

	Method 1	Method 2	Method 3	Visual 1	Visual 2
Total number of oscillations detected by each method					
Ripples	14	51	156	94	205
F-Ripples	25	80	125	113	192
Total	39	131	281	207	397
Total number of oscillations detected by each method during pre-ictal period					
Ripples	5	19	32	42	74
F-Ripples	14	32	23	33	62
Total	19	51	55	75	136
Total number of oscillations detected by each method during ictal period					
Ripples	9	26	112	40	117
F-Ripples	10	40	76	66	106
Total	19	66	188	106	213
Total number of oscillations detected by each method during post-ictal period					
Ripples	0	6	12	12	14
F-Ripples	1	8	26	14	24
Total	1	14	38	26	38