Editorial

In search of epileptic scalp high-frequency oscillations

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In this issue of *Clinical Neurophysiology* van Klink and colleagues investigate the occurrence of high-frequency oscillations (HFO) in the ripple range (80–250 Hz) in simultaneous EEG-MEG recordings (van Klink et al., 2019). Shortly summarized the manuscript's main findings suggest that MEG ripples are less frequent but more specific than EEG ripples and that both event-types provide complementary information. Beyond these straightforward observations the manuscript holds the potential of opening up several traditional battlegrounds in the world of epileptology and HFO research. Should we rely on visual identification or push for automatic detection of HFO? Is the analysis of distinct HFO equal or complementary to measuring changes in high-frequency activity (HFA)? How much postprocessing of the data is reasonable and clinically feasible? Last but not least is EEG or MEG the better technology to identify epileptic areas? From a clinician's point of view all these questions come down to whether scalp HFO are a useful tool in the day to day evaluation of patients with epilepsy. In other words will HFO help us give a prognosis in a certain patient or identify the patient's epileptogenic brain tissue? Moreover is it easy enough to find these HFO so that we will use them? This editorial aims to shortly discuss these questions in the light of the present manuscript.

To start, this manuscript is the first to compare the occurrence of HFO using simultaneous EEG-MEG recordings in a group of patients. Clearly the use of simultaneously recorded data is the only possible way allowing a direct comparison of HFO visibility between the two techniques. Up to now, most reports on scalp HFO have focused on one of the two methods (Nissen et al., 2016; Migliorelli et al., 2017; Gong et al., 2018). In one paper EEG and MEG HFO were compared in the same patients but at different points in time (von Ellenrieder et al., 2016b). This naturally may lead to significant differences in EEG and MEG ripples as occurrence of HFO might be influenced by vigilance state, time of the day and seizure propensity. Therefore the authors in the present study chose the best possible method for comparison even if this might have come with some disadvantages regarding the identification of HFO. Combined recordings usually result in a suboptimal technical setup for either one of the recording techniques. In the present case the EEG setup was most likely adapted to the MEG setting. Thus EEG was recorded with a high-density EEG cap which often results in increased impedances over time and reduced signal quality. In some settings, e.g. if the patients are lying down, the pressure on the electrode sites might also vary.

Overall the noise level in each of the measurements might be the most important factor in the analysis of scalp HFO. Especially on the scalp, HFO are often of low amplitude and defined as an event that arises from the background activity (Andrade-Valenca et al., 2011). Thus a low noise level especially in the high-frequency range of the EEG will be essential for any visual or automatic detections of HFO. One advantage of the MEG setting might be that MEG signals are so vulnerable to environmental noise that they are usually placed in a protected environment. Nevertheless, van Klink has shown before that identification of ripples still is subject to a noise problem, which can be improved by postprocessing the data (van Klink et al., 2016a).

In a situation with unclear signal to noise ratios the first question to raise is whether we should rely on visual identification or push for automatic detection of HFO. 306 MEG sensors and 60 EEG electrodes are the numbers in the current manuscript. Especially for the EEG, high-density settings are becoming more and more used in presurgical scenarios (Nemtsas et al., 2017), but even higher numbers of channels per patient are easy to imagine. Simulated data as well as simultaneous recordings of intracranial and scalp EEG suggest that the likelihood of identifying HFO on scalp increases with the number of electrodes analyzed (Zelmann et al., 2014; von Ellenrieder et al., 2016a). In a direct comparison between 21 and 128 analyzed scalp contacts, HFO were more frequent and more specific to the seizure onset zone (SOZ) in a high-density EEG setting (Kuhnke et al., 2018). Additionally, rates of events are substantially lower in scalp than in intracranial recordings (Andrade-Valenca et al., 2011; Zelmann et al., 2014). While some of the intracranial data relies on only a few minutes of EEG to find significant differences between areas inside and outside the SOZ, most scalp studies focus on a minimum of 30 min of recordings to identify enough HFO to be clinically meaningful. As a result, visual identification of HFO in the scalp setting seems even less feasible that in the intracranial EEG in either a research or clinical setting. Nevertheless designing a reliable scalp HFO detector is challenging (Zelmann et al., 2012; Thomschewski et al., 2019) and most authors like van Klink rely on a combined approach that mostly aims to exclude false positives. In the current manuscript the authors also decided to add what they called "missed ripples". These are events that were automatically detected in only one of the recording modalities and found in the other during visual confirmation. Overall, missed ripples were most often found in the EEG at points where the MEG showed an event. Missed ripples were frequently found only in three patients suggesting that in these the automatic detection might be less sensitive than in the other patients. As pointed out by the authors, inclusion of missed ripples of course introduces a bias towards time points when the detector

identifies events in one but not the other recording type. It also suggests that while visual verification can reduce false positives, the problem of false negatives cannot be solved that easily. As in all automatic detection methods sensitivity and specificity of a detector will be subject of the background noise level and event amplitude and therefore might largely vary between recording sites and even individual patients. Thus at the current point it is clear that automatic detection is a necessity for researchers and clinicians but there is vast room for improvement of detection techniques and a long way to go until clinical use.

An alternative technique to the identification of isolated HFO in the past has been the detection of HFA, opening room for the next question of this editorial: Is the analysis of distinct HFO equal or complementary to measuring changes in HFA? Many readers might not be fully aware of this discussion and its implications. Early on in the research on HFO, methods were developed to identify high-frequency components of the EEG using spectral analysis (Xiang et al., 2009b, 2009a). The major advantage of this process is a facilitated identification of events that allows processing long data periods or many data point at a time. This has been done for interictal time points including analyzing the high-frequency (HF) component of epileptic spikes as well as for ictal episodes. A large part of the existing MEG data on high-frequency activity in epilepsy has been using this method (Thomschewski et al., 2019). All these methods aim to exclude events with an increase in broadband activity, as they are likely to be artifacts or at least not distinct high-frequency events. Nevertheless it is very likely that the HF component of the signal even if the analysis is limited to narrowband events does not only consist of what would be defined as a distinct HFO event. For intracranial EEG only partial overlap between regions with increased HF activity during epileptic spikes and distinct HFO could be seen (Jacobs et al., 2016). Distinct HFO seemed more specific for the SOZ. In scalp EEG and MEG the clinical value of HF components seems similar even if no direct comparison has been performed (Thomschewski et al., 2019). Several papers have shown that inter-ictal and ictal HFA predominantly occurs over the SOZ, epileptic lesions and inside of the resection volume prior to epilepsy surgery (Kobayashi et al., 2004; Guggisberg et al., 2008; Xiang et al., 2009c). Overall more than half of the literature on epileptic high frequencies using MEG relies on automatic analysis of HFA. In a situation with an unclear noise level and many sensors the use of HF analysis is by far more straightforward than a combination of automatic detection and visual verification as used in the current manuscript. It however remains to be demonstrated that the clinical importance of HFA is equivalent to that of HFO.

Postprocessing of signals is very common in the MEG community and less frequent when reading EEGs. For the clinical use it is important to discuss the question of how much postprocessing of the data is reasonable and clinically feasible. Most clinicians will look at EEG traces just as they appear on the screen and processing usually does not go beyond defining displays for a set of standardized montages, while it is rather unusual to look at raw MEG signals. Many methodological developments for postprocessing signals, automated analysis, averaging events and source reconstruction have been developed for MEG and then afterward been translated to use in high-density EEG settings (van Klink et al., 2018). This is also true for the main methodological development presented in this manuscript. Earlier, van Klink and coworkers have demonstrated that the use of virtual sensors can improve the visualization of MEG ripples (van Klink et al., 2016a). The used beamformer technology is designed for MEG signals and available as a toolbox (Oostenveld et al., 2011), still the necessary data preprocessing including reconstruction in the MRI space is substantial (Whalen et al., 2008). In principal the calculated virtual sensors are placed on the cortical surface, an approach that many clinicians might

not be familiar with. Van Klink now applied and adapted this method also for the simultaneously recorded EEG data. For both modalities the authors provide comparisons between HFO over virtual and real sensor signals. Impressive 89% of EEG ripples and 80% of MEG ripples are only visible in the virtual sensors and would not have been seen without preprocessing and reconstruction of the raw data. The gain of information achieved by moving into the virtual space seems to be even greater in EEG than MEG signals. This is a great example how a methodology developed for one of the two techniques can be translated to the other. Reasons for the substantial gain are most likely found in the signal-to-noise ratio of the raw signal and the recorded HFO. Adding virtual cortical sensors allows to significantly reduce the amount of noise in the data and thus is especially helpful in noisy data or when looking at small-amplitude events like HFO (van Klink et al., 2016a). Like all solutions in the virtual space, the present methods also rely on a set of assumptions regarding the signal compositions, and like all methods related to source localization, beamforming faces the problem of inverse solutions. In principle, solutions are better the more information about anatomy and signals are fed to the algorithm. Van Klink states that the work in virtual space requires a lot of mostly computational work, but of course these computations have to be adapted and initialized. Any type of simplification of the preprocessing might jeopardize the data quality and reliability. Preprocessing itself might therefore be an obstacle to identifying HFO in a clinical setting. In general it seems preferable to improve the signal-to-noise ratio by improving signal quality itself. Some studies suggest that the use of subcutaneous electrodes or low-noise amplifiers (von Ellenrieder et al., 2016a; Fedele et al., 2017) might lead to decreased noise levels and better detectability of HFO. These hardware adaptations however are limited to selected research institutions and in most situations HFO will have to be recorded with whatever EEG or MEG machine can be found onsite.

It is a long-lasting discussion whether EEG or MEG is the better technology to identify epileptic areas and this will of course not be finally solved here. In general, MEG is limited to specialized centers and most patients will primarily and repetitively receive EEG recordings. Moreover, due to the use of high-density systems, EEG spatial resolution comes closer to that seen in MEG. In epilepsy the detectability of epileptic spikes has been excessively discussed with the overall conclusion that epileptic spikes with a mainly radial orientation, generated in the crown of a gyrus or bottom of a sulcus is better seen by EEG (Haueisen et al., 2012). On contrary epileptic spikes with a tangential orientation generated in the wall of a gyrus might only be seen by MEG. It is unclear whether these observations on epileptic spikes can be transferred to HFO, which probably have a very different generator size and noise level. Simultaneous scalp and intracranial EEG recordings suggest that the detectability of HFO on the scalp is largely different from that of epileptic spikes (Zelmann et al., 2014). The visibility of HFO in MEG and EEG might therefore also be different from spikes. The current study suggests that EEG sees more but MEG "better" HFO when it comes to the localization of epileptic tissue. If one oversimplifies the rules above, this would mean that tangentially generated HFO are more specific that radial ones and MEG would be the better tool for analyzing ripples. Two main challenges of the study should prevent us from such conclusions. First the patient groups are small and heterogeneous. It might be that EEG or MEG is better in finding HFO under a specific clinical constellation. Patients with a superficially located focal cortical dysplasia might profit from one modality, patients with mesial temporal lobe epilepsy from another. Larger scale studies with more homogeneous patient populations could be collected with simultaneous recordings in the future to clarify this question. Second it remains unclear whether the used beamformer method for generating the virtual sensor data is similarly reliable in both recording modali-

ties. EEG and MEG are each specifically vulnerable to different types of noise and artefacts and the reconstructed signal might be more reliable in one than the other modality. For now it seems that the most important messages might be that both modalities reliably display HFO, that EEG postprocessing improves HFO visibility and that, currently, it might be worth looking at both to gain complimentary information.

Last but not least: Are scalp HFO ready to be a clinical tool?

It is exciting that by now the visibility of HFO on the scalp has been shown by several studies (Thomschewski et al., 2019). Considering the small generator size of these oscillations and what we have known about the visibility of epileptic spikes on the scalp it has been far from self-evident that HFO could be measured non-invasively. This opens up opportunities to not only localize epileptic tissue with HFO but also investigate HFO as a biomarker of seizure propensity, treatment success and prognosis (Kobayashi et al., 2015; van Klink et al., 2016b). Looking at hardware and software developments over the last years, HFO toolboxes including automatic detection algorithms, postprocessing and source localization steps will soon become available for everybody's use. While currently most of the toolboxes only provide some support and do not have the easy-to-use quality of commercial products, some companies have started implementing HFO analysis in their clinician friendly software packages. It seems likely that the demand for a certain tool will result in supply just as manufacturers of amplifiers have long stopped wondering about the question which maximum sampling rate their amplifier can record. It however will stay in the responsibility of each clinical user to verify the performance of each tool on their own data. This might be a challenge for some users, considering that HFO analysis is either used in an oversimplified way or limited to specialized epilepsy center as has been seen for other tools like source localization.

When it comes to the EEG and MEG comparison, all the above reasons converge towards one conclusion. For the use of MEG, superiority to EEG analysis would have to be clearly demonstrated. MEG is costly, has restricted accessibility, and serial investigations are limited. The paper of van Klink gives a first indication that MEG superiority for HFO investigation might be worth it. Solid evidence will only come from larger, more homogenous patient groups which by itself might be challenging considering MEG availability.

Conflict of interest

The authors declared that there is no conflict of interest.

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References

Andrade-Valenca LP, Dubeau F, Mari F, Zelmann R, Gotman J. Interictal scalp fast oscillations as a marker of the seizure onset zone. Neurology 2011;77 (6):524–31.

Fedele T, Ramantani G, Burnos S, Hilfiker P, Curio G, Grunwald T, et al. Prediction of seizure outcome improved by fast ripples detected in low-noise intraoperative corticogram. Clin Neurophysiol 2017;128(7):1220–6.

Gong P, Xue J, Qian P, Yang H, Liu X, Cai L, Bian K, Yang Z. Scalp-recorded high-frequency oscillations in childhood epileptic encephalopathy with continuous spike-and-wave during sleep with different etiologies. Brain Dev 2018;40 (4):299–310.

Guggisberg AG, Kirsch HE, Mantle MM, Barbaro NM, Nagarajan SS. Fast oscillations associated with interictal spikes localize the epileptogenic zone in patients with partial epilepsy. Neuroimage 2008;39(2):661–8.

Haueisen J, Funke M, Güllmar D, Eichardt R. Tangential and radial epileptic spike activity: different sensitivity in EEG and MEG. J Clin Neurophysiol 2012;29 (4):327–32.

Jacobs J, Vogt C, LeVan P, Zelmann R, Gotman J, Kobayashi K. The identification of distinct high-frequency oscillations during spikes delineates the seizure onset zone better than high-frequency spectral power changes. Clin Neurophysiol 2016;127(1):129–42.

Kobayashi K, Akiyama T, Oka M, Endoh F, Yoshinaga H. A storm of fast (40–150Hz) oscillations hypsarrhythmia in West syndrome. Ann Neurol 2015;77(1):58–67.

Kobayashi K, Oka M, Akiyama T, Inoue T, Abiru K, Ogino T, et al. Very fast rhythmic activity on scalp EEG associated with epileptic spasms. Epilepsia 2004;45 (5):488–96.

Kuhnke N, Schwind J, Dümpelmann M, Mader M, Schulze-Bonhage A, Jacobs J. High frequency oscillations in the ripple band (80–250 Hz) in scalp EEG: higher density of electrodes allows for better localization of the seizure onset zone. Brain Topogr 2018;31(6):1059–72.

Migliorelli C, Alonso JF, Romero S, Nowak R, Russi A, Mañanas MA. Automated detection of epileptic ripples in MEG using beamformer-based virtual sensors. J Neural Eng 2017;14(4).

Nemtsas P, Birot G, Pittau F, Michel CM, Schaller K, Vulliemoz S, et al. Source localization of ictal epileptic activity based on high-density scalp EEG data. Epilepsia 2017;58(6):1027–36.

Nissen IA, van Klink NE, Zijlmans M, Stam CJ, Hillebrand A. Brain areas with epileptic high frequency oscillations are functionally isolated in MEG virtual electrode networks. Clin Neurophysiol 2016;127(7):2581–91.

Oostenveld R, Fries P, Maris E, Schoffelen J-M. FieldTrip: open source software for advanced analysis of MEG, EEG, and invasive electrophysiological data. Comput Intell Neurosci 2011;2011:1–9.

Thomschewski A, Hincapié A-S, Frauscher B. Localization of the epileptogenic zone using high frequency oscillations. Front Neurol 2019;10:94.

van Klink N, Hillebrand A, Zijlmans M. Identification of epileptic high frequency oscillations in the time domain by using MEG beamformer-based virtual sensors. Clin Neurophysiol 2016;127(1):197–208.

van Klink N, Mol A, Ferrier C, Hillebrand A, Huiskamp G, Zijlmans M. Beamforming applied to surface EEG improves ripple visibility. Clin Neurophysiol 2018;129 (1):101–11.

van Klink NEC, van't Klooster MA, Leijten FSS, Jacobs J, Braun KPJ, Zijlmans M. Ripples on rolandic spikes: a marker of epilepsy severity. Epilepsia 2016;57 (7):1179–89.

van Klink N, Mooij A, Huiskamp G, Ferrier C, Braun K, Hillebrand A, et al. Simultaneous MEG and EEG to detect ripples in people with focal epilepsy. Clin Neurophysiol 2019;130:1175–83.

von Ellenrieder N, Dan J, Frauscher B, Gotman J. Sparse asynchronous cortical generators can produce measurable scalp EEG signals. Neuroimage 2016;138:123–33.

von Ellenrieder N, Pellegrino G, Hedrich T, Gotman J, Lina JM, Grova C, et al. Detection and magnetic source imaging of fast oscillations (40–160 Hz) recorded with magnetoencephalography in focal epilepsy patients. Brain Topogr 2016;29(2):218–31.

Whalen C, Maclin EL, Fabiani M, Gratton G. Validation of a method for coregistering scalp recording locations with 3D structural MR images. Hum Brain Mapp 2008;29(11):1288–301.

Xiang J, Chen Y, Wang Y, Liu Y, Fujiwara H, Hemasilpin N, et al. Noninvasive detection and localization of pathologic high-frequency oscillation in tuberous sclerosis complex with waveletbased beamformer. Epilepsia 2009a;50:177–8.

Xiang J, Liu Y, Wang Y, Kirtman EG, Kotecha R, Chen Y, et al. Frequency and spatial characteristics of high-frequency neuromagnetic signals in childhood epilepsy. Epileptic Disord 2009b;11(2):113–25.

Xiang J, Wang Y, Chen Y, Liu Y, Kotecha R, Huo X, et al. Noninvasive localization of epileptogenic zones with ictal high-frequency neuromagnetic signals. J Neurosurg Pediatr 2009c;5(1):113–22.

Zelmann R, Lina JM, Schulze-Bonhage A, Gotman J, Jacobs J. Scalp EEG is not a blur: It can see high frequency oscillations although their generators are small. Brain Topogr 2014;27(5):683–704.

Zelmann R, Mari F, Jacobs J, Zijlmans M, Dubeau F, Gotman J. A comparison between detectors of high frequency oscillations. Clin Neurophysiol 2012;123(1):106–16.

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