Ann Neurol. Author manuscript; available in PMC 2013 August 27.

Published in final edited form as:
Ann Neurol. 2012 February ; 71(2): 169–178. doi:10.1002/ana.22548.

High-Frequency Oscillations as a New Biomarker in Epilepsy

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Abstract

The discovery that electroencephalography (EEG) contains useful information at frequencies above the traditional 80Hz limit has had a profound impact on our understanding of brain function. In epilepsy, high-frequency oscillations (HFOs, >80Hz) have proven particularly important and useful. This literature review describes the morphology, clinical meaning, and pathophysiology of epileptic HFOs. To record HFOs, the intracranial EEG needs to be sampled at least at 2,000Hz. The oscillatory events can be visualized by applying a high-pass filter and increasing the time and amplitude scales, or EEG time-frequency maps can show the amount of high-frequency activity. HFOs appear excellent markers for the epileptogenic zone. In patients with focal epilepsy who can benefit from surgery, invasive EEG is often required to identify the epileptic cortex, but current information is sometimes inadequate. Removal of brain tissue generating HFOs has been related to better postsurgical outcome than removing the seizure onset zone, indicating that HFOs may mark cortex that needs to be removed to achieve seizure control. The pathophysiology of epileptic HFOs is challenging, probably involving populations of neurons firing asynchronously. They differ from physiological HFOs in not being paced by rhythmic inhibitory activity and in their possible origin from population spikes. Their link to the epileptogenic zone argues that their study will teach us much about the pathophysiology of epileptogenesis and ictogenesis. HFOs show promise for improving surgical outcome and accelerating intracranial EEG investigations. Their potential needs to be assessed by future research.

A new biomarker for epileptogenic tissue has emerged, which holds the promise to improve understanding of the pathophysiology of epilepsy and to develop new clinical diagnostic methods. It is remarkable that this biomarker can be found in brief intracranial

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Potential Conflicts of Interest

P.J. has received grant(s) and has grants/grants pending from Epilepsy Research UK. J.G.R.J. has received grant(s) from the Medical Research Council (UK) and Epilepsy Research UK, and has received support for travel to the European Epilepsy Congress from UCB. M.Z. has received grant(s) from the Netherlands Organization for Scientific Research. J.G. has received grant(s) from the Canadian Institutes of Health Research; has had consultancies with Blackrock Microsystems; and has been employed by Stellate Systems. R.Z. has received grant(s) from the Natural Sciences and Engineering Research Council of Canada (NSERC-PGSD) and the Canadian Institutes of Health Research (CIHR).

electroencephalography (EEG) recordings and possibly even in extracranial magnetoencephalography (MEG) or EEG. It consists of high-frequency oscillations (HFOs) above 80Hz, which require the EEG to be sampled at a frequency above the usual 200Hz or 500Hz. Although a glimpse was perceived early,[1–3] HFOs were explored more thoroughly after they were recorded with microelectrodes in epileptic rats and in patients,[4,5] and this expanded when they were found with clinical macroelectrodes.[6,7]

In epilepsy surgery, removal of tissue with HFOs seems to predict good surgical outcome, even better than removal of the ictal onset zone.[8] This suggests that HFOs should be taken into account for clinical evaluations. This is feasible, because HFOs can be visualized and detected relatively easily. Neurologists involved in epilepsy surgery should become aware of how recording HFOs can help answer the questions they are confronted with. This review focuses on 3 aspects of epileptic HFOs: their pathophysiology, clinical relevance, and ways to identify and interpret them.

Epileptic HFOs

Epileptic high-frequency activity (HF activity) includes pathological activities with frequencies above 80Hz recorded in epileptic brain in vitro, in animals and in human patients. This includes activities of distinct frequency, morphology, underlying pathophysiological mechanisms, and clinical significance. Isolated HF oscillatory events are the most common type of HF activity and are called HFOs (Fig 1). At present, HFOs are further sub-classified in ripples (80–250Hz) and fast ripples (250–600Hz).[5,6,9–11] Different studies use slightly different bands. Recently, epileptic very-high-frequency oscillations (above 1,000Hz) have been added to the spectrum.[12] HFOs have been observed between seizures, at seizure onset, and during seizures. Interictal HFOs mostly occur during slow-wave sleep.[6,13,14] Most studies recorded HFOs from mesiotemporal structures, but they are also found in neocortex.[15]

Cellular and Network Mechanisms Generating Epileptic HFOs

Each individual cycle of a pathological HFO appears to represent co-firing of small groups of principal cells, which are pathologically interconnected.[16,17] Morphological, molecular, and functional changes in epileptic tissue cause neurons to respond abnormally to subthreshold stimuli or become spontaneously active. Single-neuronal firing (or firing of a small neuronal population) may result in fast recruitment of interconnected cells, resulting in synchronous action potential firing. This will manifest as an HFO in extracellular recordings. HFOs are generated locally and synchronizing mechanisms must be fast enough to synchronize activity within 2 ms to 5 ms. Candidate mechanisms are: ephaptic interactions,[18,19] electrotonic coupling via gap junctions,[20–22] or fast synaptic transmission.[23] Synchronous HFOs occur mostly in a spatially continuous zone, but can sometimes be detected simultaneously on contacts separated by large distances.[24]

Another feature is that epileptic HFOs, particularly fast ripples, represent activity of several populations of neurons each firing at lower frequency than the recorded HFO. A new theory suggests that these fast ripples result from out-of-phase firing of neuronal populations due to

structural, molecular, and functional changes in epileptic tissue, such as cell loss, increased synaptic noise, or acquired channelopathies.[17,25,26]

Normal neuronal circuits can generate epileptic HFOs under specific conditions (increased extracellular potassium, decreased extracellular calcium, blocked inhibition), but more in the ripple band.[23,27,28] Fast ripples were described only in animals[29–31] and patients[11] and in vitro only in slices from chronic epileptic animals.[17,32] Therefore, the presence of fast ripples probably reflects functional epileptogenic reorganization.

Mechanisms involved in HFO formation may play a role in the pathophysiology of epilepsy and seizure genesis. Their presence is a reliable marker of future development of spontaneous and recurrent seizures in rats.[29] Fast ripples have been suggested to play a role in epileptogenesis. The presence of HF activity at seizure onset suggests that it may also be involved in seizure genesis.[30,33,34] It has been demonstrated that fast ripples are generated by small independent neuronal clusters of hyperexcitable principal cells. Blocking of inhibition results in spatial expansion of HFOs,[35] which suggests that their activity and spatial extent is controlled by local inhibition. If inhibition is insufficient, activity in these independent neuronal clusters may synchronize, coalesce and result in epileptic seizures.

Physiological and Epileptic HFOs

Epileptic HFOs overlap with physiological HFOs in the ripple and fast ripple bands. Physiological ripples (~200Hz) were primarily described in the CA1 region of the hippocampus and entorhinal cortex, where ripples constitute part of the sharp-wave-ripple complex,[36] but have also been described elsewhere. Mesiotemporal HFOs are involved in memory formation and reactivation of previous experiences. Low amplitude physiological HF activity in extratemporal neocortex seems related with information processing functions, such as during somatosensory evoked potentials (~600Hz).[37]

Cellular mechanisms of gamma activity and physiological ripples differ from mechanisms involved in the generation of epileptic HF activity. Gamma activity results from a sequence of synchronous inhibitory and excitatory postsynaptic potentials on the membrane of principal cells[38] and physiological ripples result from synchronous inhibitory postsynaptic potentials on pyramidal cells.[39] Specific regional and laminar distribution of physiological HFOs, their shape, and other properties allow distinction from epileptic HFOs in experimental settings, when recorded using microelectrodes.[5,9,16,40] However, in clinical settings and recorded with macroelectrodes, it may be challenging to reliably distinguish between physiological and pathological activity, particularly in the ripple band.

HFOs in Presurgical Evaluation

The contemporary concept of presurgical examination is based on identifying the epileptogenic zone—the area of brain that needs to be removed (or disconnected) to gain complete seizure freedom.[41] The epileptogenic zone is a theoretical construct and at the moment there is no clear marker (functional or structural) that can exactly delineate it. Presurgical localization of the epileptogenic zone is based on identifying other zones that are spatially related to the epileptogenic zone: the irritative zone, the seizure onset zone, the

epileptogenic lesion, and the functional deficit zone. The identification of HFOs appears capable of improving presurgical diagnosis and surgical outcome, and it seems reasonable to add a ripple and fast ripple zone to the presurgical diagnosis.[8,15] Together, these zones create 1 HFO zone. Is it important to differentiate between ripples and fast ripples? The answer is yes, because ripples and fast ripples seem to have different pathophysiological mechanisms and can provide additive information about the epileptogenic zone. Different studies led to somewhat conflicting conclusions on the relation of ripples and fast ripples to the epileptogenic region (Table). These discrepancies may depend on the methodology. Studies with microelectrodes mostly concluded that fast ripples are most specific for the epileptogenic region. With macroelectrodes, it was often concluded that ripples *and* fast ripples are related to the epileptogenic region. Spatially, fast ripples are recorded in small areas of cortex, whereas ripples are more widespread, which might explain different findings among electrode sizes.[42]

The majority of early studies evaluated the specificity of HFOs for the diseased hippocampus in bitemporal epilepsy. Work on HFOs in mesiotemporal lobe epilepsy showed experimentally and clinically that the rate of fast ripples is significantly higher in epileptic hippocampus (see Table). However, in patients with bitemporal epilepsy, the rate of ripples *and* fast ripples was increased in the main seizure onset zone (microelectrodes and macro-electrodes).[42] Other clinical studies included patients with extratemporal epilepsy and related ripples and fast ripples to the seizure onset zone. Good postsurgical outcome has even been related more with the amount of ripples in the removed brain tissue than with the amount of fast ripples.[8]

In conclusion, several studies with microelectrodes conclude that fast ripples are most specific for the epileptogenic zone, but in clinical studies with macroelectrodes it is useful to include both ripples and fast ripples in the evaluation of the potential epileptogenic region and future studies are needed to explore the importance of discriminating between the two.

HFOs and the Irritative Zone

The irritative zone is the area of cortex generating interictal discharges (spikes). It overlaps with the epileptogenic zone and it is accepted that it is not necessary to remove the entire irritative zone, but including part of it often helps to achieve a better outcome. HFOs can occur in isolation but are often superimposed on interictal spikes. HFOs superimposed on spikes have longer duration than HFOs outside spikes.[43] Currently it is not known whether it is beneficial to distinguish between HFOs with and without spikes.

Not every interictal discharge is associated with an HFO. In general, the HFO zone, especially that of fast ripples, has smaller spatial extent than the irritative zone. It was suggested that the presence of HFOs may discriminate between so called “green” and “red” spikes, generated in epileptogenic cortex.[44,45]

The localization of HFOs remains relatively fixed over a long period with disease[46] and under different circumstances.[47,48] In contrast, interictal spikes are more labile.

HFOs and the Seizure Onset Zone

The seizure onset zone is the area where seizures originate and in certain cases it involves areas of cortex of early propagation. In the majority of surgical cases the seizure onset zone is included in the resection, but removing the entire seizure onset zone does not always result in successful surgical outcome. One explanation is that different seizures can originate from different areas within the epileptogenic zone, and the recorded seizure onsets may not represent the full extent of the epileptogenic area. Another difficulty can result from early seizure spread or seizure onset with a widespread spike, making the definition of the seizure onset zone difficult.

One of the strengths of interictal HFOs is that they have been shown to be reliable markers of the seizure onset zone, better than epileptic spikes.[5,9,13,43,49] Further confirmation of this observation may result in decreased necessity to record seizures during invasive monitoring, possibly decreasing the duration of invasive recording and the probability of complications. Besides occurring in the region of onset of spontaneous seizures, HFOs occur in regions where the threshold is low for cortical stimulation to give rise to after-discharges or evoked seizures, even outside the seizure onset zone. This suggests a correlation of HFOs with endogenous epileptogenicity.[50]

Seizures also contain HFOs. What is the clinical relevance of ictal onset HFOs? Ictal onset HFOs are somewhat more specific for the seizure onset zone than interictal HFOs, but occur mostly in similar channels.[48] Ripples and fast ripples occur at seizure onset. In mesiotemporal lobe epilepsy ictal fast ripples can precede ripples and can exceed 500Hz at seizure onset, suggesting that faster activity is involved with the seizure initiation.[51] In the tetanus toxin model of mesiotemporal lobe epilepsy the mean frequency of ictal onset HFOs is higher in the seizure onset zone and slower or absent in areas of propagation.[30] In humans, the recruitment of ictal HFOs may precede clinical symptoms and the resection of sites with early HFO augmentation has been related to good post-surgical outcome.[52] Evaluating seizures at the frequency spectrum above 80Hz can improve the clinical presurgical workup.[1,2,48,53–55] It is conceivable that ictal onset HF activity predicts surgical outcome better than the seizure onset zone defined based on low frequencies.

HFOs and the Epileptogenic Lesion

The epileptogenic lesion is a structural brain abnormality that causes epileptic seizures. The presence of an obvious structural lesion close to the irritative and seizure onset zone helps to identify the epileptogenic area and improve postsurgical outcome. HFOs occur in different types of epilepsy. Initially they were described mainly in temporal lobe epilepsy associated with hippocampal sclerosis.[4,5,9] However, HFOs are also present in extratemporal epilepsies associated with different types of lesions, such as tumors, focal cortical dysplasias, and nodular heterotopias. HFOs are related to the seizure onset zone, independently of the location and type of lesion and are therefore thought to represent the tissue's intrinsic epileptogenicity.[56,57] HFOs even occur in epilepsy without an obvious lesion.[30] Nonlesional epilepsies represent a future challenge for improvement of epilepsy surgery and HFOs could help localize the epileptogenic zone in this type of epilepsy.

How Can HFOs Be Visualized and Detected?

HFOs can be recorded with different types of intracranial electrodes: microelectrodes and macroelectrodes and with depth and subdural electrodes (corticography).[6,9,24,58–60] However, the measured signal can differ between electrode sizes.[42] The EEG needs to be sampled at about 4 times the upper frequency of interest, because it requires several samples to form the wave shape. Preferentially, a sample frequency of 2,000Hz or above should be used.

HFOs can sometimes be recognized in the unfiltered EEG.[7,30] To visualize HFOs better, a high-pass filter is applied and the EEG amplitude is increased. Recorded with macroelectrodes and after filtering, HFOs have been defined as: events with at least 4 consecutive oscillations between 80Hz and 500Hz that clearly rise above baseline.[61] Another definition has been: a root mean square amplitude increase of more than 5 times the standard deviation compared to background EEG, a duration of at least 6ms and more than 6 peaks (positive plus negative) greater than 3 standard deviations above mean baseline.[11]

One has to be aware that by applying a high-pass filter, sharp events reveal their HF components and result in occurrence of “false” ripple activity. It can be difficult to distinguish this type of HF activity HFO from stand-alone oscillations.[62] Inadequate filter parameters may also contribute to filtering artifact and occurrence of false HFO.

An alternative way to visualize the frequency content of HFOs is to build the frequency power spectrum with a Fourier or wavelet transform. This allows the separation of a stand-alone oscillation from the HF component of a sharp transient.[24,63] Changes in HF activity around epileptic spikes can be studied by statistical comparisons to the surrounding background.[63]

HFOs can be marked visually, but this manual procedure is highly time consuming and subjective, although it is possible to ensure a certain level of interrater consistency.[61] Given that HFOs are short oscillatory events that stand out from the baseline, a logical approach to identify them is applying an energy-based detector. Automatic detection methods are being developed based on the comparison of the local energy of the signal with the whole EEG epoch (including HFOs or with marked baseline segments.[11,24,64–67] When comparing the performance of these detectors, the behavior is similar in channels where HFOs are rare events that can be clearly distinguished from the surrounding background. However, in channels with very frequent HFOs the use of baseline segments to calculate the energy threshold improves the detection.[67] All automatic methods involve the human validation of automatically detected events. Development of robust and online automatic detectors is essential for the systematic study of HFOs and clinical use. The required recording time could be shortened and detection can become easier if, instead of waiting for spontaneous HFOs, we can reliably evoke pathological HFOs by electrical stimulation having characteristics similar to that of spontaneously occurring HFOs.[68]

Practical Considerations

The evidence above indicates that it may be time to include HFO information in the clinical workup of epilepsy surgery patients in specialized epilepsy surgery centers. What should be the approach and use of HFOs in presurgical diagnosis? Prospective research should prove whether preoperatively recorded HFOs might guide the neurosurgeon. We suggest that specialized epilepsy surgery clinics record the intracranial EEGs at sample frequency above 2,000Hz, look for high-pass filters that enable the visualization of HFOs and build up experience with this information (Fig 2).

The ideal electrode size still needs to be established, but it seems that any clinically used electrode can record HFOs. First, one needs to adjust the EEG amplifier settings. Some systems will not allow the higher sampling rate or allow only a limited number of channels. High sample rates will produce large data amounts, but only a short recording is needed (preferentially artifact-free recording during at least 10 minutes slow-wave sleep). High sampling rate recordings can be made after all other (seizure) information has been obtained at low sample frequencies. HFOs can be reviewed by making power spectra or by reviewing the filtered EEG data. A single electrode or common average referential montage can result in a bad signal on all channels if the reference contains HF artifacts, a problem that is avoided using bipolar montages. The filter settings of some EEG programs may not suit the requirements and might have to be adjusted by the EEG software manufacturers. At the Montreal Neurological Institute high-order high-pass finite impulse response (FIR) filters are used (80Hz and 250Hz). The FIR filter does not create a phase distortion in the remaining signal despite its high order and great filtering effectiveness (see Fig 2). The time scale can be extended to show all samples (~0.6 seconds/page) and the amplitude scale changed to $1\mu V$/mm (procedure is described at http://apps.mni.mcgill.ca/research/gotman/2000HZ.html). A channel with continuous artifacts is often recognized because the amplitude of the artifactual baseline activity is greater than the baseline activity in other channels. Other continuous artifacts originate from the main frequency (50Hz or 60Hz and harmonics); they are easily recognized by assessing the frequency. Muscle artifacts occur mostly on channels close to the skull and appear to be waxing and waning. Reviewing suspected channels simultaneously with epidural or extracranial channels at 10 to 20 seconds per page will reveal clear muscle artifact, because the activity will occur at similar times.[48] The frequency distribution of muscle activity might differ from HFOs[69] and can be distinguished in the filtered signal because the muscle HF activity looks less smooth than epileptic HFOs. Noncontinuous isolated artifacts, as those occurring during surgery when the electrodes are touched or stimulated, can be recognized because they show a sharp (high amplitude) peaks within the filtered signal. Another clue comes from artifacts occurring simultaneously at multiple channels and one has to be cautious to mark an HFO as epileptic if there is a simultaneous artifact in other electrodes. It is useful to build up experience with judging filtered EEG before drawing clinical conclusions.

Now that the HFOs can be identified, what to do next? It is still unknown to what extent the area showing HFOs should be included in the resected region. Areas showing very frequent events are probably more relevant than areas with sporadic events.[8] It is probably worthwhile to include the ripple and fast ripple zones in the set of clinical data and compare

them to the known lesional, seizure onset, and irritative zones and make a weighted decision about the epileptogenic area. The HFO zones might already replace the irritative zone in the presurgical decisions, especially in areas where the irritative zone is often widespread, such as in frontal lobe epilepsy.

Can We Diagnose or Monitor Epilepsy Using HFOs?

Although spontaneous fast ripples seem to occur mostly in the epileptic brain, they are yet not suited for diagnosis or monitoring of epilepsy, because they require invasive recordings. Noninvasive signals such as MEG and scalp EEG can be recorded at higher sample frequency but the electrodes might be too far away from the source or the signal might be blurred by background noise and muscle activity. However, HFOs have been seen on scalp EEG and MEG correlated to spikes and seizures.[70–72] Also, independent of spikes and seizures, HFOs in the lower-ripple range have been found in sleep EEG of children and adults with epilepsy.[73] A recent study reports that gamma and ripple activity can often be recorded from the scalp in patients with focal epilepsy, can be separated from short EMG bursts, and is better correlated with the seizure onset zone than interictal spikes.[74]

The ability to record HFOs on the scalp would open new possibilities of diagnosing epilepsy. In several rat models of epilepsy, HFOs occur during the latent period before the first spontaneous seizures.[29,31] Moreover, all the animals in which HFOs occurred developed spontaneous seizures.[29] It was suggested that epileptic HFOs and particularly fast ripples could be used as biomarkers of epileptogenesis. If recorded noninvasively, they could be used clinically as an early marker of future development of epilepsy in high-risk patients (for example after traumatic brain injury).

HFOs could be used as a marker of response to antiepileptic drug therapy. Withdrawal of antiepileptic medication, which increases the chance of having seizures, results in an increase in the number of HFOs.[47] HFOs seem to increase during the period directly preceding seizures and increase further around seizure onset.[27,48,58,75–77] Their number does not change after seizures. The increase of HFOs with an increase in seizure risk suggests that HFOs are a marker of disease activity. In other words, HFOs seem not only a spatial marker of the focus of epileptogenicity, but also a temporal marker for epileptic intensity. HFOs could be useful to evaluate treatment effect.

Conclusion and Future Directions

HFOs appear to be new markers of the extent and intensity of epileptogenicity. The time has come for specialized epilepsy surgery centers to record intracranial EEG at high sampling rates and to evaluate it for HFOs. It will provide the neurophysiologist information about the extent of the epileptogenic tissue in addition to ictal and interictal lower frequency information. Fast ripples probably result from structural tissue changes, whereas ripples may signify a broader area of normal appearing tissue with a low seizure-generation threshold. Both ripples and fast ripples are important to consider. Prospective studies are needed to show if real-time processing of HFOs can guide neurosurgeons in the removal of

epileptogenic tissue, hopefully improving surgical outcome and reducing the need for traditional long-term recordings.

Acknowledgments

This research was supported by grants from the Canadian Institutes of Health Research (MOP 102710; RZ, JG); Netherlands Organization for Scientific Research (NWO) (AGIKO 92003481; MZ); Epilepsy Research UK (A0937; PJ); MRC (G0802162; JGRJ).

We thank Dr P. Marusic for his comments on the manuscript.

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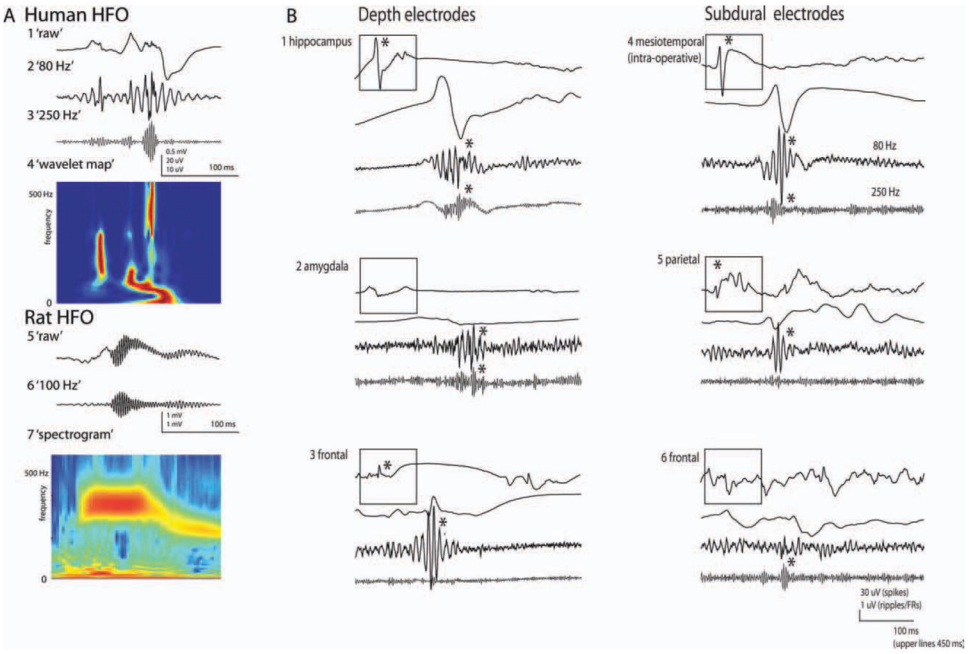

FIGURE 1.

Examples of HFOs. (A) HFOs recorded with depth macroelectrode in human (1–4) and rat (5–7) hippocampal area. (1) Raw intracranial EEG with sharp wave from human hippocampal area (macroelectrode). (2 and 3) Filtered with high-pass filter of 80Hz and 250Hz. Note the differences in amplitude scales. Such an event would not stand out in normal EEG. (4) Wavelet transform of frequencies up to 500Hz. (5) Raw intracranial EEG data from rat with right intrahippocampal injection of tetanus toxin (microelectrode). A fast ripple with peak frequency 359Hz followed by activity at 240Hz is visible in the raw data. (6) Filtered with high-pass filter of 100Hz. (7) Spectrogram up to 500Hz after Fourier transformation. (B) HFOs recorded with depth and subdural macroelectrodes, in mesiotemporal areas and neocortical areas in patients with epilepsy. For each event the display shows the standard EEG signal, the same signal with extended time scale and this signal after 80Hz and 250Hz high-pass filtering. Different examples are shown from different sites. This illustrates that all combinations are possible: spike with ripple and fast ripple (1+4), ripple and fast ripple without spike (2), spike with ripple without fast ripple (3+5) and fast ripple without ripple or spike (6). An asterisk (*) means that the event was marked at this frequency. EEG = electroencephalogram; FRs = fast ripples; HFO = high-frequency oscillation.

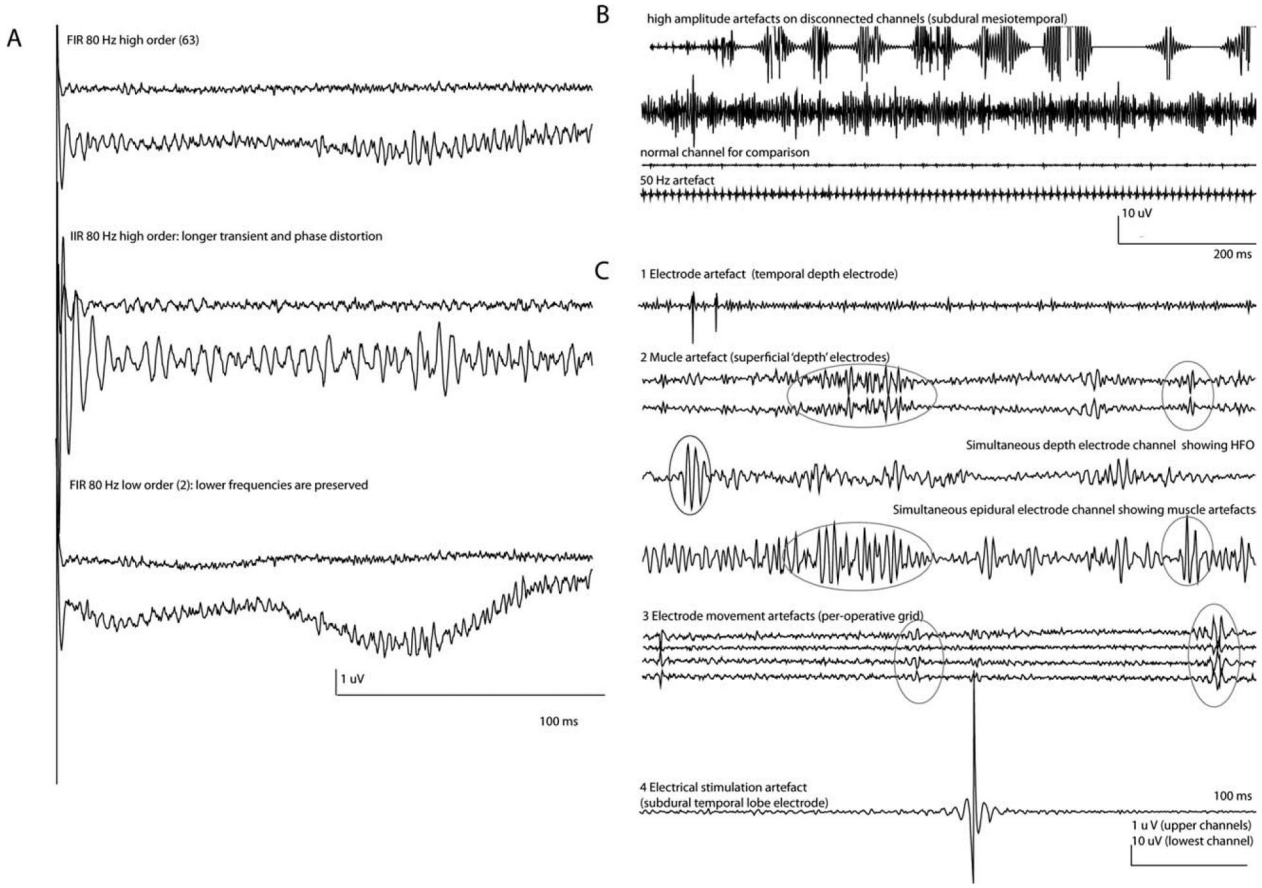

FIGURE 2.

Examples of EEG patterns and problems that can be encountered when filtering the EEG with a high-pass filter. (A) Baseline signal. First, 2 temporal neocortical channels with high-order FIR high-pass filter of 80Hz, extension of time and amplitude of 1μV/mm are shown. This is how the baseline should look. The period is shown from recording onset and shows the transient response of the filter (time required for the filter to settle). The same 2 channels are shown after IIR high-pass filter. In contrast to the FIR filter, the IIR filter has a longer transient response at the beginning of the trace and is not as effective in removing activity below 80Hz. IIR filters can be made more effective by increasing their order but IIR filters of high order can create important phase distortions, thus making the signal difficult to recognize. Beneath the channels are shown with a FIR low-order high-pass filter, where lower frequencies are not as well removed compared to a higher-order filter. Beneath the channels are shown with a FIR low-order high-pass filter, where lower frequencies are preserved compared to high order. The low-frequency drift makes the channels hard to assess, especially because with longer recording periods and with more activity the drift becomes even greater. (B) Examples of continuous artifacts that can be encountered. Channel 1 and 2 show channels with loose electrode connections. The third channel is a normal neocortical channel for comparison. Note that the amplitude is 10 times lower than the (normal) examples shown in A. The last channel shows artifact at 50Hz and harmonics, which can be recognized because of the regular pattern. (C) Examples of short-lasting

artifacts. (1) The first channel shows a sharp artifact in a malfunctioning channel. Usually these artifacts are very sharp, which is not seen in regular baseline or HFOs. (2) The second and third channel show muscle artifact. This can be difficult to distinguish from HFOs (fourth channel), but can be recognized because it occurs repeatedly and simultaneously on channels that are superficial; ie, close to the skull (fifth channel). Also, muscle artifacts often show a less regular pattern than HFOs. (3) The 4 channels show short-lasting artifacts due to preoperative movement of the electrodes. This is hard to distinguish from HFO, but only happens during surgery and can then be noted. Also, the artifact can be recognized as it occurs over multiple channels and has sharp components. (4) Artifact due to a single-pulse stimulation of the electrode. Note the greater amplitude. EEG = electroencephalogram; FIR = finite impulse response; HFO = high-frequency oscillation; IIR = infinite impulse response.

TABLE

Studies Comparing Interictal Ripples and FRs to the Potential Epileptogenic Region

Study	Subjects	Site	Electrodes	Epileptogenicity Parameter	Study Conclusion
Bragin and colleagues (1999)[5,9]	Rats (KA) and human	MT	Micro	Epileptic individuals and seizure onset side	FRs
Bragin and colleagues (2002)[35]	Human	MT	Micro	Multiunit neuronal synchronization	FRs
Bragin and colleagues (2004)[29]	Rats (KA)	MT	Micro	Side of KA injection, having seizures	Both
Staba and colleagues (2004/2002/2007)[11,13,78]	Human	MT	Micro	Seizure onset side and region atrophy	FRs
Urrestarazu and colleagues (2006)[49]	Human	MT/F	Macro	Seizure onset zone	FRs
Jacobs and colleagues (2008)[43]	Human	MT/F	Macro	Seizure onset zone	FRs > ripples
Worrell and colleagues (2008)[42]	Human	MT	Micro and macro	Seizure onset zone	Both
Jacobs and colleagues (2010/2009)[50,56]; Zijlmans and colleagues (2011)[48]	Human	MT/F/P/O	Macro	After discharges and seizure onset zone	Both
Ogren and colleagues (2009)[79]	Human	MT	Micro	Hippocampal atrophy	FRs
Jiruska and colleagues (2010)[30]	Rats (TT)	MT	Micro	Side of injection	FRs > ripples
Jacobs and colleagues (2010)[8]	Human	MT/F/O	Macro	Surgical outcome	Ripples > FRs

The conclusion describes whether fast ripples or ripples were more specific for the presumed epileptogenic area or whether no clear difference was found.

F = frontal; FR = fast ripple; KA = kainic acid; MT = mesiotemporal; O = occipital; P = parietal; TT = tetanus toxin.