



# High-Frequency Activity During Stereotyped Low-Frequency Events Might Help to Identify the Seizure Onset Zone

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## Stereotyped high-frequency oscillations discriminate seizure onset zones and critical functional cortex in focal epilepsy.

Liu S, Gurses C, Sha Z, Quach MM, Sencer A, Bebek N, et al. *Brain*. 2018;141(3):713-730. doi:10.1093/brain/awx374. PMID: 29394328.

High-frequency oscillations in local field potentials recorded with intracranial electroencephalogram are putative biomarkers of seizure-onset zones in epileptic brain. However, localized 80- to 500-Hz oscillations can also be recorded from normal and nonepileptic cerebral structures. When defined only by rate or frequency, physiological high-frequency oscillations are indistinguishable from pathological ones that limit their application in epilepsy presurgical planning. We hypothesized that pathological high-frequency oscillations occur in a repetitive fashion with a similar waveform morphology that specifically indicates seizure onset zones. We investigated the waveform patterns of automatically detected high-frequency oscillations in 13 patients with epilepsy and 5 control subjects, with an average of 73 subdural and intracerebral electrodes recorded per patient. The repetitive oscillatory waveforms were identified using a pipeline of unsupervised machine learning techniques and were then correlated with independently clinician-defined seizure onset zones. Consistently in all patients, the stereotypical high-frequency oscillations with the highest degree of waveform similarity were localized within the seizure onset zones only, whereas the channels generating high-frequency oscillations embedded in random waveforms were found in the functional regions independent of the epileptogenic locations. The repetitive waveform pattern was more evident in fast ripples compared to ripples, suggesting a potential association between waveform repetition and the underlying pathological network. Our findings provided a new tool for the interpretation of pathological high-frequency oscillations that can be efficiently applied to distinguish seizure onset zones from functionally important sites, which is a critical step toward the translation of these signature events into valid clinical biomarkers.

## Commentary

Ripples, fast ripples, high-frequency oscillations (HFOs), high-frequency activity, pathological HFOs, physiological HFOs, and phase-locked HFOs. These are just some of the more commonly used terms to classify fast electrical activity in the brain. These subtle delineations are of clinical importance. Over two decades of concerted research has shown that distinct HFOs, if carefully analyzed and classified, might help to identify the bounds of the seizure onset zone in patients with intractable focal epilepsies.<sup>1-4</sup> Improved HFO classification thus has the potential to help optimize surgical resection and improve post-surgical outcome.<sup>5</sup> A recent article by Liu et al, published in *Brain*, adds “stereotyped HFOs” to the list of HFO delineations and suggests that stereotyped HFOs are effective biomarkers of the seizure onset zone. The results are promising, with high sensitivity and accuracy metrics, suggesting that the automated methodological advances made by Liu et al should be carefully compared to and perhaps combined with existing HFO analysis and classification methods. However, as discussed below, the

term “stereotyped HFOs,” without additional context, can be easily misinterpreted in terms of its conceptual and physiological implications.

It is instructive to begin with a brief recap of ripples and their relationship with sharp waves in the CA1 region of the healthy rodent hippocampus. These CA1 ripples are physiological HFOs in the 100-250 Hz range that occur during non-rapid eye movement sleep and quiet wakefulness and are important for the consolidation of memories.<sup>6,7</sup> Such ripples are typically generated by strong, synchronous, excitatory synaptic inputs from CA3 onto CA1 neurons. This first causes ionotropic glutamate receptors to open, leading to positive ions rushing into the CA1 neurons and depolarizing them. If an extracellular electrode is precisely positioned in the vicinity of these synapses, then it will pick up a large, slow, initially negative deflection, reflecting the net movement of positive ions from the extracellular space into local neurons. This deflection is the start of the sharp wave. Near the trough of this sharp wave, some CA1 cells, including inhibitory neurons, get



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depolarized enough to fire action potentials. This fast, inhibition-dominated network activity then generates an HFO that can be seen on the extracellular electrode if it is positioned close enough to the cell bodies. Such physiological HFOs are true rhythmic oscillations: the firing of excitatory neurons is paced by periodic inhibition recurring every  $\sim 5$  milliseconds, giving rise to the characteristic  $\sim 200$  Hz frequency of healthy ripples.<sup>7,8</sup> Changing the exact depth of the electrode can alter the appearance of the sharp-wave ripple events: Some locations emphasize the low-frequency sharp waves (whose polarity also changes with depth), whereas others may reveal just the high-frequency ripples. Thus, the precise position of the electrode with respect to the location of the synapses and cell bodies can determine how many ripples are seen and how consistently the ripples appear to be time-locked to the sharp waves.

Fast ripples are often defined as events having frequencies in the 250-500 Hz range. When multiple action potentials are fired in rapid succession by a handful of neurons, this random sequence can be picked up as high-frequency activity (HFA) on a nearby electrode. However, such HFA is rarely truly rhythmic: it does not have to be paced by periodic inhibition to still appear as a very high-frequency event. The lack of true rhythmicity is also why we prefer to use the term HFA instead of HFO to describe this type of high-frequency event. The pseudo-synchronous firing of enough action potentials sufficient to generate an HFA event can happen in healthy neural circuits but is more likely in a more active circuit with pathologically impaired inhibition.<sup>8,9</sup> For this reason, fast ripples are thought to be more prevalent in epileptic areas than in healthy brain regions. However, separating HFOs/HFA simply based on their frequency is not always enough to delineate which high-frequency events are physiological versus pathological: not all events in the 100-250 Hz ripple frequency range are physiological, and not all events in the  $>250$  Hz fast ripple frequency range are pathological. Like healthy ripples, fast ripples typically need some sort of synaptic drive to generate them and are thus likely to show similar associations to slower interictal spikes or sharp waves as those discussed earlier for sharp-wave ripples. An electrode may thus record fast ripples on their own, interictal spikes on their own, or the co-occurrence of fast ripples with interictal spikes.

Manual identification is often used to identify HFOs and spikes in intracranial recordings from patients with epilepsy. However, this process can be extremely time consuming and not completely unbiased. For this reason, Liu et al used an automated, unsupervised set of algorithms to identify high-frequency events on every electrode recorded during a 60 minute awake period from 13 patients with either temporal lobe or extratemporal neocortical focal epilepsy. They also analyzed intraoperative data from 5 patients with brain tumors but with no history of seizures. Their methods included separating out high-frequency artifacts corresponding to spike-related transients. The seizure onset zone was visually identified by neurologists in 11 of the patients with epilepsy, and functional cortex (motor, sensory, or language related) was demarcated using direct cortical mapping in 5 of the patients with epilepsy as

well as all of the patients with brain tumors. With these anatomical labels in place, they were then able to compare the properties of the automatically detected HFOs in the seizure onset zone (sHFO) to those seen in functional cortices (fHFO). While the rate of sHFOs was higher than that of fHFOs, this difference was not significant. However, the rate of sHFOs was much higher than the rate of HFOs from regions that were neither in the seizure onset zone nor in the functional areas, consistent with previous findings.<sup>2</sup> Using a clustering algorithm that has been used in many fields (DBSCAN: density-based spatial clustering of applications with noise), the authors then looked to see how similar sHFOs were to other sHFOs and how similar fHFOs were to other fHFOs. In other words, how stereotyped were the HFOs in each category? They found that sHFOs were much more likely to form clusters of events with very similar appearances. The most stereotyped sHFO events were found to involve fast ripples rather than ripples. The HFOs in functional cortex were far less likely to display such stereotypy. The authors thus propose that the proportion of stereotyped HFOs on a given electrode might help to identify the seizure onset zone.

What gives rise to this stereotypy? A critical point to note is that the high-frequency band is not itself stereotyped as might be assumed upon first hearing the term “stereotyped HFO.” It is very rare for any two fast ripples to look identical (i.e., stereotyped), especially considering that they are thought to represent the pseudo-synchronous, almost random, firing of neurons. Instead, the stereotypy is due to the co-occurrence of HFOs with their underlying slow synaptic drive: fast ripples may not be stereotyped, but, in the seizure onset zone, a subset of fast ripples co-occur with stereotyped low-frequency events such as interictal spikes or sharp waves (see their Figure 4 for clear examples). When phrased this way, the results of Liu et al are mechanistically similar to previous work showing that HFOs in seizure onset zones are more likely to show phase-amplitude coupling to low-frequency spikes or sharp waves.<sup>2,4,10</sup> High-frequency oscillations in seizure onset zones being phase-locked to their underlying low-frequency events is thus the key biomarker that is consistent across these studies. Future work should ideally combine the excellent unsupervised clustering methods of Liu et al with phase-amplitude coupling methods<sup>4,10</sup> across both sleep and wake states to comprehensively understand exactly how the two analysis techniques complement each other. Given the challenges and immense importance of HFO classification,<sup>5</sup> such hybrid and transparent approaches are likely to yield the most clinical benefits in terms of identifying the seizure onset zone with very high sensitivity and accuracy.

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