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Is it time to replace epileptic spikes with fast ripples?

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In well over a century of performing epilepsy surgery, only 60%–65% of patients are, on average, seizure-free postoperatively.¹ Despite multiple advances in neuroimaging and electrophysiologic techniques for localizing the epileptogenic zone and determining its boundaries, defining the exact amount of neuronal tissue required to resect in order to achieve postoperative seizure freedom remains challenging. The quest for a reliable biomarker of the epileptogenic zone continues. In addition to long-term intracranial EEG recordings to identify the seizure onset zone, cortical resections are also tailored in the operating room by including areas with abundant epileptic spikes and seizure-like interictal activity (ictiform patterns) recorded with corticography.² Intraoperative localization based on interictal EEG activity would be much more cost-effective than chronic recording to capture spontaneous seizures.

In this issue of *Neurology*®, van 't Klooster et al.³ retrospectively studied high-frequency oscillations (HFO) as a biomarker of the epileptogenic zone during intraoperative electrocorticography. They reviewed the occurrence of HFOs after resection of an epileptogenic lesion, mainly glial tumors and cortical malformations, in 54 young patients. HFOs included ripples, defined as oscillations between 75 Hz and 250 Hz, and fast ripples (FR), defined as oscillations between 250 Hz and 500 Hz. Ripples are normal electrographic events recorded from hippocampus and may reflect summated inhibitory postsynaptic potentials that synchronize neurons over wide areas and facilitate information transfer.^{4–6} FR, on the other hand, are pathologic events, believed to reflect summated action potentials of synchronously bursting neurons indicative of epileptogenic tissue capable of generating spontaneous seizures.^{4–6} This distinction is not absolute, however, as ripple frequency HFOs in dentate gyrus are pathologic, and presumably other ripple frequency oscillations also reflect pathologic action potentials of synchronously bursting neurons, while FR frequency oscillations can be normal in neocortex.^{4–6}

HFOs are distinct events that are short in duration, stand out from the background, and consist of more than 4 oscillations. When reporting on HFOs, it is important to clearly define their frequency, as done in this study.³ HFOs occur at the same time or separate from other epileptiform activity such as sharp waves and epileptic spikes.⁵ van 't Klooster et al. clearly distinguished FR from ripples with and without associated spikes. They found that the presence of FR after removal of the presumed epileptogenic lesion correlated with a worse seizure outcome after surgery. In many of the patients, the persistent FR were recorded from brain tissue that could have easily been included in the resection. Persistence of ripples, spikes, and other epileptiform discharges did not correlate with seizure outcome. Results were consistent for FR with spikes but not for FR without spikes, which may be an effect of low sample size. The authors concluded that intraoperative FR could be used to tailor cortical resections.

Many workers have correlated resection of tissue exhibiting preoperatively recorded HFOs with surgical outcome and found later removal of both FR and ripples to be predictive of seizure freedom.^{7–11} This study is the first to correlate post-resection HFOs with surgical outcome. However, whether resection of residual FR-generating areas would have made a difference in outcome remains speculative and needs to be confirmed by prospective studies.

This study is consistent with the view that FRs are reliable biomarkers for the epileptogenic zone which, if true, could provide a simple solution for a longstanding clinical problem. However, there are many remaining questions about HFOs. The importance of ripples and FRs, as biomarkers, likely differs between hippocampal and neocortical brain regions.^{7–11} There may also be a difference introduced by recording electrode size and placement; for instance, dipole configuration of pathologic and normal ripple frequency oscillations may make the former more easily recorded by large clinical electrodes, explaining why they appear to localize

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the epileptogenic region in some studies.⁹ Spatial and temporal characteristics, therefore, may be important in the effort to distinguish pathologic from nonpathologic HFOs.¹²

van 't Klooster et al. warn that FR could also be a marker of physiologic functional tissue. HFOs are markers for normal cognitive, visual, and somatosensory processing.⁴ In animal models, HFO are particularly important in episodic memory processing.⁴ It is of importance to distinguish HFOs as distinct burst-like events in contrast to continuous HFO activity during cognitive processing that is locked to stimulus events.^{4,13}

The value of recording interictal spikes with electrocorticography as a biomarker to tailor resections has been disputed.² van 't Klooster et al. confirmed that spikes are not a good biomarker for the epileptogenic zone, and their removal is not correlated with a good seizure outcome. Perhaps it is time to focus on HFOs, which appear to be reliable biomarkers under appropriate recording conditions. Recording FR intraoperatively requires EEG acquisition with a high sampling rate that is now offered by most EEG equipment vendors. Automatic detection algorithms have been developed.¹⁴ van 't Klooster et al. employed a supervised detection algorithm, with initial automatic detection and later visual confirmation. Nevertheless, this is still labor intensive, especially as it may be difficult to quantify the occurrence of HFOs in one channel as compared to another. With our current signal processing capabilities and machine-learning advances, it should not be difficult to develop user-friendly systems for clinical practice in the near future. More research is also necessary to elucidate the underlying fundamental neuronal mechanisms responsible for generating HFOs, not only to improve their value as biomarkers, but to identify potential targets for novel approaches to treat seizures and prevent and cure epilepsy.

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