

## ARE ICTAL FAST RIPPLES AN “ELECTRONIC SIGNATURE” FOR THE SEIZURE-ONSET ZONE?

**High-Frequency Oscillations during Human Focal Seizures.** Jirsch JD, Urrestarazu E, LeVan P, Olivier A, Dubeau F, Gotman J. *Brain* 2006;129(Pt 6):1593–1608. Discrete high-frequency oscillations (HFOs) in the range of 100–500 Hz have previously been recorded in human epileptic brains using depth microelectrodes. We describe, for the first time, similar oscillations in a cohort of unselected focal epileptic patients implanted with EEG macroelectrodes. Spectral analysis and visual inspection techniques were used to study seizures from 10 consecutive patients undergoing presurgical evaluation for medically refractory focal epilepsy. Four of these patients had focal seizure onset in the mesial temporal lobe, and in all 12 of their seizures, well-localized, segmental, very high frequency band (VHF 250–500 Hz) oscillations were visually identified near the time of seizure onset from contacts in this zone. Increased high-frequency band (HF 100–200 Hz) activity compared with the background was distinguished both visually and with spectral analysis later in the seizures of 3/4 mesial temporal patients, involving contacts in the generator region and, in one patient, areas of contralateral perihippocampal propagation. Three patients with well-defined neocortical seizure-onset areas also demonstrated focal HF or VHF oscillations confined to the seizure-onset channels during their eight seizures. No discrete HF or VHF activity was present in the poorly localized seizures from the remaining three patients. These results show that discrete HFOs can be recorded from human focal epileptic brain using depth macroelectrodes, and that they occur mostly in regions of primary epileptogenesis and rarely in regions of secondary spread. Absent high-frequency activity seems to indicate poor localization, whereas the presence of focal HFOs near the time of seizure onset may signify proximity to the epileptogenic focus in mesial temporal lobe and neocortical seizures. We postulate that focal HFOs recorded with depth macroelectrodes reflect the partial synchronization of very local oscillations such as those previously studied using microelectrodes, and result from interconnected small neuronal ensembles. Our finding that localized HFOs occur in varying anatomical structures and pathological conditions perhaps indicates commonality to diverse epileptogenic etiologies.

### COMMENTARY

When neurosurgical treatment of medically refractory focal epilepsy is considered, the site of seizure origination is often identified by concordance of localizing information from neuroimaging studies and noninvasive EEG recordings. In many cases, however, this information is inadequate, and invasive EEG recording of seizures, using intracranial subdural, depth, or epidural electrodes, is needed to identify the zone of seizure onset. Interpretation of invasive ictal recordings can be challenging, both because electrical abnormalities may be widespread and because surgically implanted electrodes may be placed in a location that does not adequately cover the seizure-onset zone. Interictal epileptiform discharges are seldom discretely localized to the region of seizure onset. When electrode arrays are not correctly placed, the electrode in which the ictal electrographic discharge first appears may only be a region of secondary propagation from an uncovered, and thereby unidentified, seizure-onset zone.

When interpreting invasive recordings, how can one be certain that the true region of seizure onset has been identified? When should the clinician suspect that only a region of secondary spread has been found? One criterion is the temporal relation between the initial behavioral seizure manifestations and the onset of the electrographic discharge. If signs or symptoms of the seizure begin before the electrical changes, surely only a region of secondary propagation has been identified. Another clue is the presence of high-frequency activity, typically in the gamma (30–80 Hz) frequency range, at the onset of the ictal electrographic discharge (1,2). Such activity, sometimes colloquially referred to as a “buzz,” has long been recognized by electroencephalographers as a useful marker of the seizure-onset zone. Yet, this phenomenon has been poorly characterized and understood, which is in part because conventional EEG recordings typically are limited to a bandwidth of approximately 0.5 to 70 Hz.

Investigation of higher-frequency bands—consisting of “ripples” (high-frequency oscillations of 80–200 Hz) and “fast ripples” (very high-frequency oscillations of 250–500 Hz)—in human focal epilepsy is compelled by an impressive body of basic research. Ripples were first recorded in CA1 hippocampal

pyramidal cells and later in entorhinal cortex; they are most prominent during non-REM sleep and are thought to have a normal, functional role (3). Both ripples and fast ripples have been recorded in experimental hippocampal and neocortical focal seizures (4,5) and in human mesial temporal epilepsy (5). In human epileptic hippocampus and entorhinal cortex, two spectrally distinct oscillations have been recorded and interpreted as representing physiological ripples and pathological fast ripples associated with epileptogenesis (6). In rats made epileptic by intrahippocampal kainate injection, stable sites of interictal fast ripples are established in the hippocampus, and the number of electrodes from which fast ripples could be recorded correlate with how often spontaneous seizures occur (7). It has been proposed that high-frequency 200-Hz oscillations in the hippocampus result from axons of depolarized hippocampal pyramidal cells, which are electrically coupled by gap junctions that phasically excite interneurons at ripple frequencies (8). Another, perhaps, complimentary mechanism, which was proposed to explain observations of recordings of experimental neocortical seizures, is that ictal fast oscillations could be a reflection of synchronous action potentials that generate strong field potentials (“field ripples”), which help produce and synchronize action potentials in an autoregenerative fashion (4). Grenier et al. also have presented evidence that ripples occur at the transition to ictal events and are involved in the mechanism of seizure initiation (4).

The experimental data cited in the previous paragraph put fast ripples at the onset of seizures, both in time and in space. In this context, the work by Jirsch et al. begins to translate these basic science findings into a useful clinical tool for seizure localization. The authors describe the recording and analysis techniques for identifying and localizing ictal ripples and fast ripples during presurgical recordings with conventional depth electrodes in human focal epilepsy. Acquisition with a low-pass filter of 500 Hz and a sampling frequency of 2,000 Hz is key. Visual inspection of the recording (with appropriate expansion of the time base and high-pass filtering) is a more informative method of identifying high- and very-high-frequency oscillations than is spectral analysis.

The work by Jirsch and colleagues convincingly demonstrates, for the first time, that it is possible to detect and localize ictal 80–400 Hz activity in human intracranial recordings using conventional depth electrodes and that this activity is found at the seizure-onset zone, as determined by analysis of the EEG at conventional frequencies. However, it has not yet been proven that the boundaries of a fast ripple zone would correspond exactly to the margins of the seizure-onset zone that should be surgically resected. It also has not yet been demonstrated that fast ripples are a universal feature of seizure foci of all etiologies.

This important preliminary research by Jirsch et al. raises several issues for future research:

1. At this point, the results only have been validated by comparison with conventional clinical determination of the seizure-onset zone, not by the “gold standard” of surgical outcomes.
2. Only 10 patients have been studied, with focal cortical dysplasia, mesial temporal atrophy, destructive gliotic lesions, or cryptogenic epilepsy—a larger number of localization-related epilepsies of diverse etiologies needs to be investigated.
3. Depth electrodes have only limited spatial sampling along a single dimension. Mapping of neocortical seizure-onset zones in two dimensions with subdural grids may help to better define the borders of the ictal electrical changes and, thereby, confirm exact colocalization of the fast ripple and seizure-onset zones. Special recording arrays with smaller, more densely placed electrodes may be necessary to reliably detect and adequately localize fast oscillations.
4. The experimental literature indicates that fast ripples are also an interictal marker of the seizure-onset zone—brief bursts of fast oscillations without associated change in behavior occur frequently in animals with kainate-induced epilepsy. Jirsch et al. only looked at fast ripples that occurred during behavioral seizures and did not examine other portions of the recording for high-frequency oscillations. If this relationship between interictal fast ripples and the seizure-onset zone also exists in human epilepsy and is robust, this finding could lead to new approaches to identifying the surgical seizure focus without ictal recording, perhaps even noninvasively, by techniques such as magnetoencephalography.

Finally, the work by Jirsch et al. provides additional evidence that the conventional EEG recording bandwidth, determined by the technical limitations of midtwentieth century recording devices, discards very valuable information. Scalp ictal recordings typically contain their highest power at infraslow (<0.5 Hz) frequencies, which can be used for ictal localizations (9). The current work now demonstrates that for invasive monitoring, recording of frequency bands in the 80–500 Hz range may not only be a practical tool to identify the seizure focus for surgical resection, but also may give new insights into mechanisms of epileptogenesis.

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