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More Is More: Potential Benefits of Characterizing High-Frequency Activity Over Long Durations

Variability in the Location of High-Frequency Oscillations During Prolonged Intracranial EEG Recordings

Gliske SV, Irwin ZT, Chestek C, et al. *Nat Commun*. 2018;9(1):2155. doi:10.1038/s41467-018-04549-2. PMID: 29858570.

The rate of interictal high-frequency oscillations (HFOs) is a promising biomarker of the seizure onset zone, though little is known about its consistency over hours to days. Here, we test whether the highest HFO-rate channels are consistent across different 10-minute segments of electroencephalography during sleep. An automated HFO detector and blind source separation are applied to nearly 3000 total hours of data from 121 subjects, including 12 control subjects without epilepsy. Although interictal HFOs are significantly correlated with the seizure onset zone, the precise localization is consistent in only 22% of patients. The remaining patients have one intermittent source (16%), different sources varying over time (45%), or insufficient HFOs (17%). Multiple HFO networks are found in patients with both one and multiple seizure foci. These results indicate that robust HFO interpretation requires prolonged analysis in context with other clinical data, rather than isolated review of short data segments.

Commentary

In patients with intractable focal epilepsy, pathological high-frequency activity (pHFA), when carefully analyzed, can help identify the seizure onset zone (SOZ).[1-4] This information, together with traditional SOZ markers, can then potentially help clinicians decide exactly what tissue should be resected to try to ensure the highest likelihood of postsurgical seizure freedom. Although pHFA clearly holds great promise as a biomarker of epileptic tissue, the correlations are not always consistent in all patients.[5] There are many potential reasons for this, including the type of epilepsy each patient has, the anatomical location and high-frequency activity (HFA)–generating capabilities of the patient-specific SOZ, the fact that it is hard to know which high-frequency events are physiological versus pathological, and the precise methods used to analyze the properties of the HFA. As discussed below, HFA—be it physiological or pathological—can be highly variable over time.[6] Despite this fact, many studies have used short 10-minute epochs of data for HFA analysis. There have been good reasons for using a short time period: it is better to manually (via the trained eyes of a human expert) verify each potential high-frequency event on each channel as being real and nonartefactual, rather than analyzing massive amounts of automated, unverified, and potentially flawed detections. However, improved automated HFA detection algorithms have made it possible to more reliably analyze longer data sets.[7-9] A recent paper by Gliske et al now uses such automated algorithms to show that there is a large degree of variation in both the timing and location of detected HFA across hours and days, emphasizing the importance of longer duration analyses before making HFA-dependent decisions regarding the SOZ.

It has long been known that the probability of hippocampal ripples—healthy high-frequency oscillations (HFOs) in the 100 to 250 Hz range—varies significantly over time.[6] In rodents, such healthy ripples are rarely seen during active movements or other motivated behaviors. Instead, they are most likely to occur during non-rapid eye movement (NREM) sleep and quiet wakefulness. Even if we only look at NREM sleep, the probability of ripples can show dramatic changes both within and across NREM epochs. Non-rapid eye movement ripple probability is strongly influenced by the duration of the previous awake period, as well as the amount of novel learning that took place before sleep.[6] Similar learning-related changes in ripple probability have also been confirmed in humans.[10] In addition, no two individual ripples are exactly alike, spanning a range of peak amplitudes and durations. Thus, the rate and appearance of even healthy ripples can vary substantially over consecutive 10-minute segments.

What about the variability of pathological HFA? Unlike healthy HFOs (such as ripples) which are paced by periodic inhibition, pHFA in epileptic tissue is more likely to arise from the pseudosynchronous, overlapping, almost random firing of multiple neurons without rhythmic pacing by inhibition.[11] These are rarely true oscillations, hence the reason for calling

them pHFA and not pathological high-frequency oscillations (pHFO). The underlying generation mechanisms mean that pHFA can often span an even wider range of frequencies and amplitudes than healthy HFOs. The probability of this random neuronal firing underlying pHFA generation is likely to vary widely and be influenced by a host of parameters that regulate neuronal excitability, including brain state, instantaneous levels of neuromodulators, and the specific circuitry and pathology in a given brain region.[12] Another crucial factor leading to variability over time is the impact of surgery. Postoperative electroencephalography (EEG) takes days, and often weeks, to stabilize after surgery in rodents.[13] Similarly, long timescales have been observed in patients implanted with long-term seizure advisory systems, preventing algorithms from accurately classifying interictal events in some patients until the intracranial EEG signal has stabilized weeks after surgery.[14] Indeed, seizures themselves have been shown to be delayed following the implantation of intracranial electrodes, compared to scalp-based EEG monitoring.[15] Thus, pHFA is almost certainly impacted by the implantation of intracranial electrodes for a period of at least 1 to 2 weeks before it returns to a presurgical baseline. Since the majority of patients undergoing phase II monitoring are implanted for less than 2 weeks, there is likely to be immense variability in this nonstationary HFA during this entire monitoring period.

Gliske et al tested the hypothesis that HFA is likely to vary significantly over both time and space. They characterized HFA from intracranial recordings in 91 patients from the Mayo Clinic and 18 patients from the University of Michigan (UM) Health System. In addition, HFA was also characterized in 12 "control" participants with chronic facial pain but with no history of epilepsy. High-frequency activity was detected using an automated algorithm developed recently by some of the same authors,[7] as well as a separate method involving Hilbert transforms. The results were qualitatively similar across detection algorithms. For each Mayo patient, a 2-hour period from 1 to 3 am was analyzed, with the assumption that the patient was mostly asleep during this time (no sleep scoring was used). The UM patients were sleep-scored and all NREM periods analyzed across several days. The rate of HFA was calculated in 10-minute chunks spanning the entire analysis duration. Blind source separation was used to group channels that had similar temporal variation patterns in their HFA rates. The aim of these procedures was to classify each patient in terms of the spatiotemporal consistency of their HFA. The key observation is both simple and important: of the 109 patients with epilepsy, only 22% had a single consistent and continuous source of HFA (category 1); 16% had a single HFA source, but the rate of HFA was intermittently either high or low over time (category 2); critically, 45% of the patients had multiple, often alternating, sources of HFA (category 3). This means that randomly choosing 10-minute HFA segments in patients from either category 2 or 3 (together representing 61% of patients) can result in inconsistent and poor correlations with the SOZ, as identified using more standard techniques. If analyzed over increasing time periods, patients would also often switch between categories, again highlighting the temporal and spatial variability of HFA during the entire phase II monitoring period. The authors rightly conclude that this means that care is needed when using HFA to identify the SOZ: more HFA data are better than less data, but even with more data, traditional clinical metrics of SOZ should be used in conjunction with HFA data to decide the resection volume.

There are some important caveats and necessary future work to keep in mind when interpreting these results. There was clear variation in the rate of HFA even in the control patients. This is consistent with the fact that even healthy HFOs vary over time and also consistent with the nonstationarity of all EEG signals for at least 1 or 2 weeks after surgery. It also highlights a key potential improvement that can be made to the analyses performed here: a more detailed attempt to characterize physiological versus pathological HFA. Since both healthy and pathological HFA can vary over time, we need a way to ask how much of the variance is specifically due to the pathological HFA. Although not an easy question to answer, there may be some important possibilities to explore. Since pHFA in SOZs is more likely to be phase-amplitude coupled to low-frequency spikes,[4,9] it would be informative to ask how this phase-locking value itself varies over long durations. Similarly, most HFA analysis protocols, including the one used by Gliske et al, typically prefer to look at HFA only during NREM sleep. However, some evidence suggests that pHFA may be more specific (compared to healthy HFOs) to epileptogenic tissue during awake and REM states.[16,17] Thus, extending these long duration analyses to multiple brain states might also help to identify the brain state that shows the least variance in HFA rate over time. If awake artefacts are a concern, then perhaps REM sleep would be an ideal period to analyze HFA variance, as it would be relatively free of movement artefacts. When it comes to HFA characterization, more data and more precise and detailed analysis are clearly the best way forward.

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