



High-Frequency Oscillations Recorded on Scalp EEG

Interictal Scalp Fast Oscillations as a Marker of the Seizure Onset Zone

Andrade-Valenca LP, Dubeau F, Mari F, Zemann R, Gotman J. *Neurology* 2011;77:524–531.

OBJECTIVE: This study aims to identify if oscillations at frequencies higher than the traditional EEG can be recorded on the scalp EEG of patients with focal epilepsy and to analyze the association of these oscillations with interictal discharges and the seizure onset zone (SOZ). **METHODS:** The scalp EEG of 15 patients with focal epilepsy was studied. We analyzed the rates of gamma (40–80 Hz) and ripple (>80 Hz) oscillations, their co-occurrence with spikes, the number of channels with fast oscillations inside and outside the SOZ, and the specificity, sensitivity, and accuracy of gamma, ripples, and spikes to determine the SOZ. **RESULTS:** Gamma and ripples frequently co-occurred with spikes (77.5% and 63% of cases). For all events, the proportion of channels with events was consistently higher inside than outside the SOZ: spikes (100% vs 70%), gamma (82% vs 33%), and ripples (48% vs 11%); $p < 0.0001$. The mean rates (events/min) were higher inside than outside the SOZ: spikes (2.64 ± 1.70 vs 0.69 ± 0.26 , $p < 0.02$), gamma (0.77 ± 0.71 vs 0.20 ± 0.25 , $p < 0.02$), and ripples (0.08 ± 0.12 vs 0.04 ± 0.09 , $p < 0.04$). The sensitivity to identify the SOZ was spikes 100%, gamma 82%, and ripples 48%; the specificity was spikes 30%, gamma 68%, and ripples 89%; and the accuracy was spikes 43%, gamma 70%, and ripples 81%. **CONCLUSION:** The rates and the proportion of channels with gamma and ripple fast oscillations are higher inside the SOZ, indicating that they can be used as interictal scalp EEG markers for the SOZ. These fast oscillations are less sensitive but much more specific and accurate than spikes to delineate the SOZ.

Commentary

Similar to many diagnostic technologies, EEG has seen significant development over the past decades. In the 1980s, digital EEG replaced analog recording methods, and with this advance wide-bandwidth EEG recordings became possible. Local field potentials recorded from the human brain have a wide dynamic range, from ultra-slow to high-frequency oscillations. Terminology for high-frequency oscillations (HFOs) is varied and often includes gamma (30–80 Hz), ripple (80–250 Hz), and fast ripple (250–1000 Hz) oscillations. There is accumulating evidence from human intracranial recordings that interictal HFOs are increased in the seizure onset zone (1) and that resection of HFO-generating tissue is associated with seizure-free outcomes (2, 3). In addition, studies from rodent epilepsy models find that HFOs are a potential biomarker of epileptogenesis (4). These results have generated intense interest because of the possible clinical impact (5), including using HFOs for interictal mapping of the epileptogenic zone (2, 3, 6) and as an electrophysiological biomarker for tracking epileptogenesis (7).

Thus, recent reports describing HFOs on scalp EEG recordings have created significant interest. In the paper discussed here (8), scalp recorded HFOs were found to be associated with epileptiform spikes and the seizure onset region in patients

with focal epilepsy. The scalp EEGs of 15 patients with focal epilepsy were studied, and the rates of gamma (40–80 Hz) and ripple (80–200 Hz) oscillations, their correlation with epileptiform spikes, and seizure onset zone were determined. The authors report gamma and ripple oscillations often occurred with spikes and were more common in the region of seizure onset. Although HFOs were less sensitive than epileptiform spikes, they were more specific and accurate predictors of the region of seizure onset. These are very interesting results and if confirmed could provide a noninvasive technique for localizing of epileptogenic brain and tracking epileptogenesis.

There are, however, multiple challenges associated with recording cerebral-generated high-frequency activity. It is useful to distinguish between actual local-field-potential (LFP) HFOs versus cerebral activity containing high-frequency spectral power (9). The analysis of HFOs is commonly focused on specific frequency bands, and various sharp transients, muscle artifact, eye movement, and electrode noise artifacts are all associated with spectral power in high-frequency bands (gamma, ripple, fast-ripple band). Even cerebral activity without actual HFOs present in the raw local field potential recording can show high-frequency spectral power after Fourier transform. The phenomena is well known, first reported more than a century ago by Gibbs (10) and commonly referred to as “Gibbs’ phenomena.” In practice, high-frequency power related to Fourier transform versus actual HFOs is relatively easy to distinguish by testing for true oscillations in the raw signal (6, 9). Although high-frequency spectral power in the Fourier transform and HFOs are often lumped together, their distinction may be important.



Muscle artifact in particular has prominent spectral power in the high-frequency bands (gamma and above, >30 Hz). Myogenic activity can be a significant challenge even for intracranial EEG (iEEG) recordings, often incorrectly assumed to be free of eye movement and muscle artifacts. Multiple studies have demonstrated that intracranial electrodes near cranial foramen and eye muscles can be contaminated by myogenic activity (11). Eye blinks, saccades, and microsaccades can contribute gamma-range increases in spectral power (12). In addition to eye movements, facial grimacing and chewing can generate prominent myogenic high-frequency spectrum artifacts on iEEG (13).

Lastly, previous studies using simultaneous scalp and iEEG report approximately 7 cm² of cortex must be involved for an epileptiform sharp wave or spike to be detected on scalp EEG (14). The fact that HFOs recorded with iEEG tend to be spatially localized and relatively low amplitude suggests they should be a challenge to detect on scalp EEG. Scalp EEG studies reporting gamma oscillations and gamma-band activity previously have primarily come from paradigms using repeated trials, thus improving signal-to-noise ratio by averaging, for example.

Digital electronics and computing have revolutionized clinical electrophysiology. The distinction between cerebral activity, muscle, and other noncerebral artifacts, however, remains a significant challenge even for iEEG, and more so for scalp EEG. The recent reports of scalp-recorded HFOs in patients with epilepsy are very important, and their verification and extension should be a top priority for clinical electroencephalography.

by Gregory Worrell, MD, PhD

References

1. Bragin A, Engel Jr J, Wilson CL, Fried I, Buzsáki G. High-frequency oscillations in human brain. *Hippocampus* 1999;9:137–142.
2. Jacobs J, Zijlmans M, Zelman R, Chatillon CE, Hall J, Olivier A, Dubeau F, Gotman J. High-frequency electroencephalographic oscillations correlate with outcome of epilepsy surgery. *Ann Neurol* 2010;67:209–220.
3. Wu JY, Sankar R, Lerner JT, Matsumoto JH, Vinters HV, Mathern GW. Removing interictal fast ripples on electrocorticography linked with seizure freedom in children. *Neurology* 2010;75:1686–1694.
4. Bragin A, Wilson CL, Engel J. Chronic epileptogenesis requires development of a network of pathologically interconnected neuron clusters: a hypothesis. *Epilepsia* 2000;41(suppl 6):S144–S152.
5. Worrell G, Gotman J. High-frequency oscillations and other electrophysiological biomarkers of epilepsy: Clinical studies. *Biomark Med* 2011;5:557–566.
6. Blanco JA, Stead M, Krieger A, Stacey W, Maus D, Marsh E, Viventi J, Lee K, Marsh R, Litt B, Worrell G. Data mining neocortical high-frequency oscillations in epilepsy and controls. *Brain* 2011;134:2948–2959.
7. Engel J, Bragin A, Staba R, Mody I. High-frequency oscillations: What is normal and what is not? *Epilepsia* 2009;50:598–604.
8. Andrade-Valenca LP, Dubeau F, Mari F, Zelman R, Gotman J. Interictal scalp fast oscillations as a marker of the seizure onset zone. *Neurology* 2011;77:524–531.
9. Bénar CG, Chauvière L, Bartolomei F, Wendling F. Pitfalls of high-pass filtering for detecting epileptic oscillations: A technical note on “false” ripples. *Clin Neurophysiol* 2010;121:301–310.
10. Gibbs J. Fourier's series. *Nature* 1899:200.
11. Jerbi K, Freyermuth S, Dalal S, Kahane P, Bertrand O, Berthoz A, Lachaux J. Saccade related gamma-band activity in intracerebral EEG: Dissociating neural from ocular muscle activity. *Brain Topogr* 2009;22:18–23.
12. Yuval-Greenberg S, Tomer O, Keren AS, Nelken I, Deouell LY. Transient induced gamma-band response in EEG as a manifestation of miniature saccades. *Neuron* 2008;58:429–441.
13. Otsubo H, Ochi A, Imai K, Akiyama T, Fujimoto A, Go C, Dirks P, Donner E. High-frequency oscillations of ictal muscle activity and epileptogenic discharges on intracranial EEG in a temporal lobe epilepsy patient. *Clin Neurophysiol* 2008;119:862–868.
14. Tao JX, Ray A, Hawes-Ebersole S, Ebersole JS. Intracranial EEG substrates of scalp EEG interictal spikes. *Epilepsia* 2005;46:669–676.



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