EPILEPSY CURRENTS

Current Literature
In Clinical Science

Toward the "Fingerprint" of the Ictal Onset Zone – Is Mr. Morlet the Winner?

A Fingerprint of the Epileptogenic Zone in Human Epilepsies.

Grinenko O, Li J, Mosher JC, Wang IZ, Bulacio JC, Gonzalez-Martinez J, Nair D, Najm I, Leahy RM, Chauvel P. *Brain* 2018;141:117–131.

Defining a bio-electrical marker for the brain area responsible for initiating a seizure remains an unsolved problem. Fast gamma activity has been identified as the most specific marker for seizure onset, but conflicting results have been reported. In this study, we describe an alternative marker, based on an objective description of interictal to ictal transition, with the aim of identifying a time-frequency pattern or 'fingerprint' that can differentiate the epileptogenic zone from areas of propagation. Seventeen patients who underwent stereoelectroencephalography were included in the study. Each had seizure onset characterized by sustained gamma activity and were seizure-free after tailored resection or laser ablation. We postulated that the epileptogenic zone was always located inside the resection region based on seizure freedom following surgery. To characterize the ictal frequency pattern, we applied the Morlet wavelet transform to data from each pair of adjacent intracerebral electrode contacts. Based on a visual assessment of the time-frequency plots, we hypothesized that a specific time-frequency pattern in the epileptogenic zone should include a combination of (i) sharp transients or spikes; preceding (ii) multiband fast activity concurrent; with (iii) suppression of lower frequencies. To test this hypothesis, we developed software that automatically extracted each of these features from the time-frequency data. We then used a support vector machine to classify each contact-pair as being within epileptogenic zone or not, based on these features. Our machine learning system identified this pattern in 15 of 17 patients. The total number of identified contacts across all patients was 64, with 58 localized inside the resected area. Subsequent quantitative analysis showed strong correlation between maximum frequency of fast activity and suppression inside the resection but not outside. We did not observe significant discrimination power using only the maximum frequency or the timing of fast activity to differentiate contacts either between resected and non-resected regions or between contacts identified as epileptogenic versus non-epileptogenic. Instead of identifying a single frequency or a single timing trait, we observed the more complex pattern described above that distinguishes the epileptogenic zone. This pattern encompasses interictal to ictal transition and may extend until seizure end. Its time-frequency characteristics can be explained in light of recent models emphasizing the role of fast inhibitory interneurons acting on pyramidal cells as a prominent mechanism in seizure triggering. The pattern clearly differentiates the epileptogenic zone from areas of propagation and, as such, represents an epileptogenic zone 'fingerprint'.

Commentary

As the authors indicate in the introduction, "Seizure onset is not a monomorphic but a complex phenomenon." While this is true, the authors probably make this complex problem more complicated by developing and implementing not-so-straightforward methods of EEG data processing without providing in-depth explanation of their choices. On the surface, they achieve a great success: They are able to combine analyses of multiple frequencies of the EEG activity into a one data processing stream that results in identification of the ictal zone "fingerprint" in 15 out of the 17 patients included in the study and in 58/64 of the EEG contacts contained in the ictal onset zone. The identified fingerprint includes three ictal patterns: preictal/initial spikes that evolve into a concurrent narrow-band fast activity with simultaneous suppression of preictal low frequency, mainly delta/theta activities. However, before fully embracing the concepts put forth by the authors, let us dive deep into the analyses.

To identify the unique attributes of the epileptogenic zone, Grinenko et al. based their hypotheses on previous work that identified both fast and slow activities as possible biomarkers of ictal onset zone (1, 2). These authors analyzed a small subsample based on very narrow criteria and selected from a large group of patients (17/280) who underwent evaluation for neocortical epilepsy surgery. To identify the previously

Epilepsy Currents, Vol. 18, No. 3 (May/June) 2018 pp. 158–159

mentioned three patterns, they utilized the Morlet wavelet transform (MWT) instead of the standard frequency analysis (Fourier Transform [FT]). While MWT has several advantages over FT, recognizing these advantages needs an understanding of the basics of both analytical methods (3). This is where the collegial relationship with a friendly biomedical engineer comes in handy. In general, MWT is similar to FT, but instead of convolving the signal with a theoretically infinite sine wave, it uses Gaussian windowed sine wave, typically with 6 to 8 cycles called the "Morlet wavelet" (sometimes called the "Gabor wavelet"). To calculate different frequencies, this wavelet should be scaled, shrunk to higher or stretched to lower frequency, and it should be shifted (and convolved) point-by-point through the entire EEG signal. The resulting 2D data should show, for every data point, the amplitude on the given scale (shrinking or stretching), which is inversely proportional to the central frequency of the wavelet; that is, with worse temporal but better frequency resolution in the lower frequencies of the EEG and better time but worse frequency resolution in the higher frequencies of the EEG. Furthermore, FT assumes that the signal frequency is stable, which is not true for EEG signals in which the frequency structure of the signal changes over time, changes occurring frequently from one second to the other. One more advantage of MWT over FT is that the frequencies in the signal can be specified by the user rather than depending on the number of data points in the signal. From these properties, we can deduce that MWT has better time-frequency resolution than does FT and is better suited for the analyses of complex EEG patterns that rarely follow simple sinusoidal distribution.

Grinienko and colleagues processed data with MWT to observe specific EEG patterns, which they found in the majority of patients in this highly selected group. After that, they built an automatic method that extracted the pre-ictal spike, ictal high and low frequencies, and their timing from every channel. These features, called "three fingerprint features," and the electrode positions were used as a machine learning method input that eventually determined whether or not a given electrode belonged to the ictal onset zone. With this method, they identified fingerprint electrodes located in the ictal onset zone defined by the margin of resection with 90.6% precision (58/64 electrodes with this pattern were inside the resection margin) and a low false positive rate of 0.7% (6/827 of fingerprint electrodes were located outside the resection margin). This potentially sounds great—high specificity and low error rate….

From an electrophysiology point of view, this study established a common link between dynamic and co-occurring changes in the EEG and outcomes for the first time, something that has been missing from the literature. Individually, these features have been studied and used for this purpose with lesser accuracy than the fingerprint proposed here. Further, the identification of the dynamic and co-occurring patterns of stereoelectroencephalography (SEEG) changes indicates that this feature could be used to identify the ictal onset zone with automated data analyses for resection planning with a potentially higher chance of seizure freedom with more limited resection (here, the most exciting case was the patient treated with very limited laser ablation). In addition, the findings indicated that there may be a specific pattern that is characteristic for the ictal onset zone removal, which could be used as a predictor of outcome. Another strength of this study is that the authors conducted a very meticulous study by merging current neurological and engineering knowledge and by sharing the methods with others.

However, here is the "spoiler alert." Unfortunately, the authors selected patients for participation in this study who had highly specific EEG characteristics based on visual analyses and with predetermined outcomes. The question that begs asking: Why did Grinienko and colleagues limit their sample to patients with specific EEG patterns and only good surgical outcomes? Wouldn't showing the failure of surgery associated with not resecting the identified pattern (e.g., due to involvement of eloquent cortex) further support the notion that the identified patterns were, in fact, ictal onset zone and that the fingerprint could be used as a biomarker? Wouldn't showing an association between the lack of the fingerprint in the EEG and not-seizure-free outcome after resection strengthen their argument?

Many questions remain to be answered before our confidence is close to certainty regarding selection of candidates for epilepsy surgery and of the cortical areas resection that offer the highest chance of seizure freedom. However, for now, we know that the chance of seizure freedom is much higher with a surgical approach when compared to the best medical therapy, and lack of certainty should not prevent us from offering this potentially curative treatment to our patients suffering from this terrible disease.

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References

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