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The Role of Delta-Modulated High Frequency Oscillations in Seizure State Classification

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Abstract— **High frequency oscillations (HFOs), which collectively refer to ripples (80–200 Hz) and fast ripples (>200 Hz), have been implicated as key players in epileptogenesis. However, their presence alone is not in and of itself indicative of a pathological brain state. Rather, spatial origins as well as coexistence with other neural rhythms are essential components in defining pathological HFOs. This study investigates how the phase of the delta rhythm (0.5–4 Hz) modulates the amplitude of HFOs during a seizure episode. Seven seizures recorded from three patients presenting with intractable temporal lobe epilepsy were obtained via intracranial electroencephalography (iEEG) from a 64-electrode grid. Delta modulation of the HFO rhythms was found to emerge at seizure onset and termination regardless of the dynamics present within the seizure episode itself. Moreover, the differences between delta modulating the ripple or fast ripple may be due to the sleep stage of the patient when the seizures were being recorded. Further studies exploring how this modulation changes in space across the grid may also highlight additional properties of this phenomenon. Its temporal pattern suggests that it is a potential iEEG-based biomarker for seizure state classification.**

I. Introduction

High frequency oscillations (HFOs) – namely, ripples (80–200 Hz) and fast ripples (>200 Hz) – have been gaining prominence over the last decade in an effort to better understand the mechanisms involved in epileptogenesis. These rhythms have been recorded both in rodents [1] and humans [2]. Their presence alone, however, is not indicative of a pathological brain. A review by Engel *et al.* [3] highlights the differences between normal HFOs and pathological HFOs and emphasizes the importance of the spatial origin of the HFOs as the distinguishing factor separating normal and pathological rhythms. Specifically, pathological ripples can be recorded from the dentate gyrus whereas normal ripples cannot. Moreover, unlike pathological fast ripples, normal fast ripples can be recorded from some areas of normal neocortex but not from the hippocampus or parahippocampal structures.

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In addition to the spatial origin of HFOs, the significance of their presence in pathological brains may also be reflected in their coexistence with other rhythms. A recent study by Nariai *et al.* [4] has shown that ripples in epileptic spasms are phase coupled with the delta rhythm. Specifically, during the ictal state ripples are tightly locked to the phase of the slow-wave at ≤1 Hz and loosely locked to that of ≥3 Hz. Moreover, this locking was reversed during interictal activity. They further suggest that this slow-wave-HFO coupling that is occurring during the ictal state may be the result of local synchronization of neocortex-generated potentials as opposed to those generated farther away by subcortical structures. A recent review by Jefferys *et al.* [5] thoroughly discusses potential underlying mechanisms of HFO generation.

The functional significance of delta rhythms (< 4Hz) in cognition and pathological brain states such as Alzheimer's, dementia, and schizophrenia is still largely unknown [6]. Studies have found that cognitive tasks elicit delta network activity, which is reduced in pathological brains such as those of Alzheimer's patients [7]. Delta rhythms have also been associated with motivation and have been found to increase in power during periods of attention or pain [6]. Moreover, during wakefulness, delta activity is often overpowered by the activity of higher frequencies but becomes more dominant when these higher frequencies are pathological. In patients with temporal lobe epilepsy (TLE), interictal regional delta slowing (IRDS) has been found to correlate with positive surgical outcomes although the underlying mechanisms responsible for this slowing are unknown [8]. Tao *et al.* [8] further suggest that IRDS can be used as an EEG marker of TLE networks.

Effectively, epilepsy is hyperexcitable state of the neural networks of the brain. During a seizure episode, when this hyperexcitability is realized, there is an overload of communication between the various regions of the brain, which is often long-range and would thus be facilitated by lower frequencies [9]. The focus of this work is to investigate the coexistence of these lower frequencies – specifically, the delta rhythm – and HFOs in epileptic human brain. Intracranial electroencephalogram (iEEG) recordings from patients with TLE were examined for modulation between delta and HFO rhythms. Specifically, phase-amplitude modulation was investigated as a potential biomarker for seizure state classification.

II. Materials and Methods

iEEG recordings were obtained from three patients presenting with intractable TLE; patient 1, 36 years old, is a female while patients 2 and 3 are males, 16- and 30-years old, respectively. All three patients have been experiencing seizures for over a decade. Informed consent was obtained

from each patient and the ethics committee of the affiliated institutions approved this study.

A. Data Acquisition

A 64-electrode grid was placed on the left, right, and right fronto-temporal lobe of patient 1, 2, and 3, respectively (Fig. 1). Recordings we sampled at 2 kHz. Differential electrodes were used for the subsequent analysis to reduce dimensionality to 32 channels and also minimize any ground artifacts that may have been present in the individual electrodes. Recordings were also downsampled to 1 kHz for computational efficiency. Power line interference at 50 Hz and all associated harmonics were notch filtered using an FIR filter with a -70 dB drop.

Three seizures were recorded from patient 1, all of which occurred during the day while she was awake and interacting with family members. Two seizures were recorded from each patient 2 and 3, all four of which occurred at night during sleep. The specific stage in sleep was not monitored. Video EEG Monitoring (VEM) provided videos alongside the iEEG recordings. These videos were used for determining seizure onset and termination.

B. Channel Selection

Channel selection was based on average wavelet phase coherence (aWPC) and time distributions. In a recent study by Cotic *et al.* [10] WPC was computed for high gamma frequencies of up to 300 Hz and averaged in time across the seizure episode as well as across all channel pairings. This resulted in patient-specific regions within the grid that exhibited high coherence (Fig. 1). The time distributions of the channels in these regions of interest (ROI) were further explored and a single channel was selected for preliminary analysis based on the visibility of the modulation in a 5 second window taken in the middle of the seizure episode. Channel 2 was selected for further analysis for patient 1 and channel 27 was selected for both patients 2 and 3.

C. Modulation Index

The remainder of the analysis focused on the modulation index (MI) within the select channels, which was computed using the algorithm proposed by Tort *et al.* [11] and the coefficients of the continuous wavelet transform (CWT) computed with a Morlet mother wavelet. Specifically, phase-amplitude modulation was investigated for phase frequencies of 0.5–10 Hz modulating amplitude frequencies of 11–450 Hz in 5 second windows (shifted by 1 second). This particular algorithm was selected due to its superior performance compared to other algorithms measuring cross-frequency coupling. Tort *et al.* [11] compare their algorithm to the heights ratio, power spectral density of the amplitude envelope, mean vector length of amplitude expressed as a complex vector, phase-locking value, correlation coefficient and its generalized counterpart, and finally the coherence spectrum between the amplitude envelope and the original signal. While these measures of phase-amplitude coupling may have their advantages, modulation index was shown to be the only one of the eight to have good tolerance to noise while remaining amplitude independent and maintaining a good sensitivity to multimodality and modulation width.

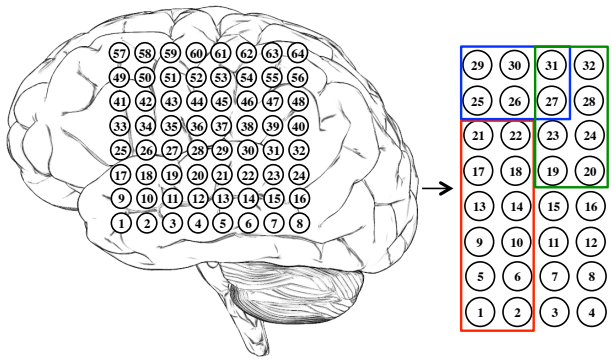

Figure 1. A 64-electrode grid was placed on the left, right, and right fronto-temporal lobe of patient 1, 2, and 3, respectively, as shown on the left. Differential electrodes were used for analysis by taking the difference between adjacent electrodes (i.e., 1–2, 3–4, 5–6, etc.), which resulted in a final 32-channel array, as shown on the right. The aWPC computed by [6] found ROIs exhibiting high coherence for patient 1 (red), patient 2 (green), and patient 3 (blue). After further investigation of the time distributions in these ROIs channel 2 was selected for analysis of patient 1 while channel 27 was selected for both patients 2 and 3.

III. Results

The bottommost panels in Fig. 2(a)–(c) illustrate the wavelet coefficients of a representative seizure from each patient. The dominating frequencies remain within the delta rhythm for patients 2 and 3. However, for patient 1, the dominating frequency transitions from a delta rhythm to theta (4–8 Hz) as the seizure progresses then back to delta again once the seizure terminates. For all three patients, the dominant low frequency is not at full strength for the full duration of the clinical seizure.

Although seizures between patients differ both in the time and frequency domains, delta modulation at seizure onset and termination is observed in all patients. Fig. 2 illustrates how this neural code identifies the seizure state in each patient. Patient 1 is the only patient out of the three to exhibit theta modulation of the 40 Hz rhythm within the seizure episode itself (middle panels of Fig. 2(a)). Additionally, theta-ripple modulation is also present. The shift of the modulating frequency from the delta to the theta rhythm is consistent with the seizing frequency of this patient, as illustrated in the bottommost panel of Fig. 2(a). Moreover, the relative strength of this seizing frequency is reflected in the modulation.

The seizures recorded from patient 2 are comparable in duration to those of patient 1. The delta rhythm appears to be modulating the ripple once again (middle panels of Fig. 2(b)). However for this patient this delta modulation is present throughout the entire seizure, not just at onset and termination. The theta rhythm does not participate in this modulation at any point during the seizure.

Patient 3 is particularly interesting and appears to have the shortest seizures of all three patients. His seizures show a brief burst of activity in the wavelet coefficient plot that is the sparsest of all three patients (bottommost panel of Fig. 2(c)). Modulation of the fast ripple by frequencies <1 Hz is observed only at the onset and termination of the seizures (middle panels of Fig. 2(c)). Apart from these two events, there is relatively no modulation present.

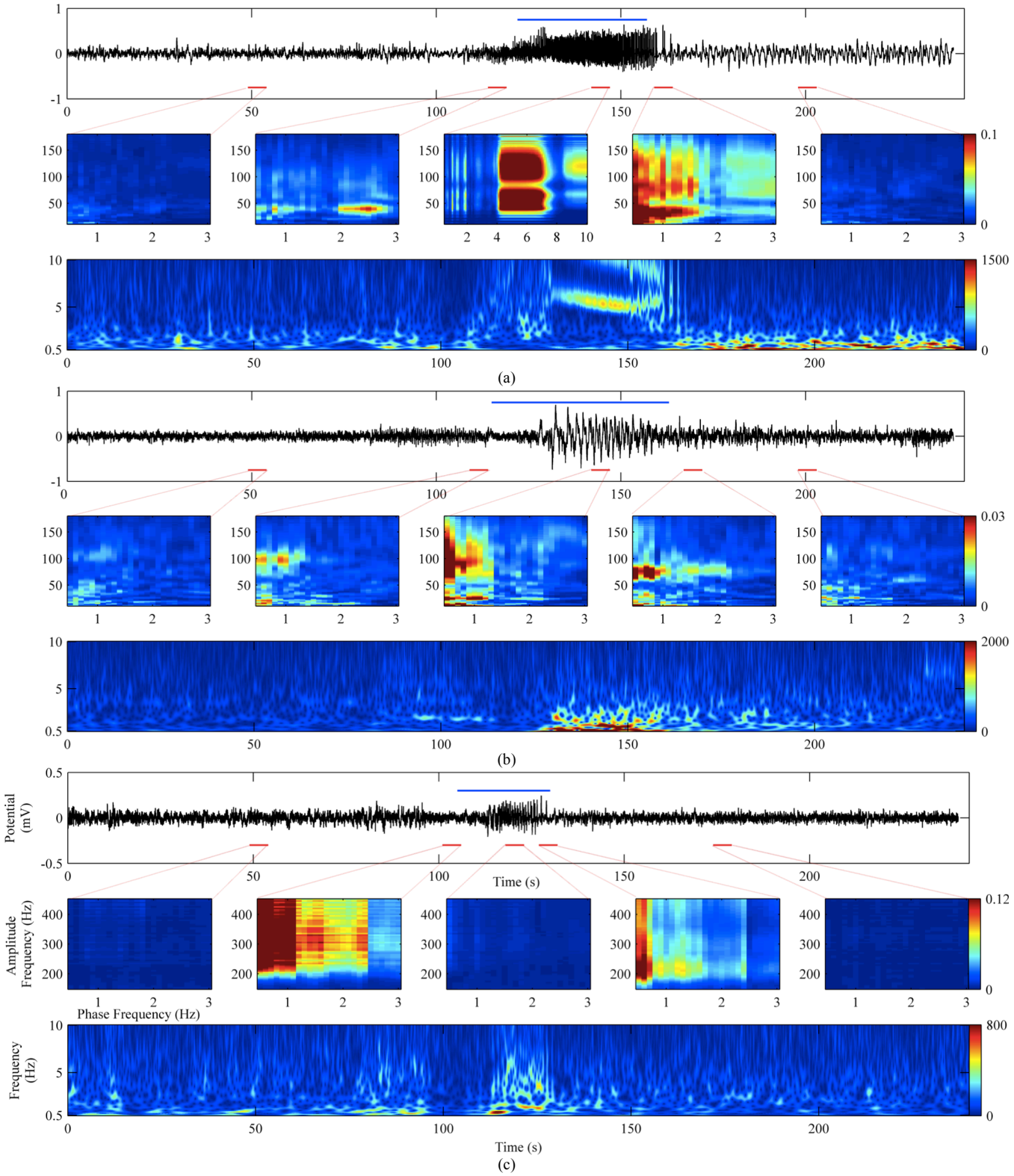

Figure 2. The CWT using a Morlet mother wavelet was computed for 0.5–450 Hz for the select channels of each patient which were then used for computing MI in 5 second windows (shifted by 1 second) for phase frequencies of 0.5–10 Hz modulating amplitude frequencies of 11–450 Hz. The results for (a) patient 1, (b) patient 2, and (c) patient 3 are summarized above. The top panel is the iEEG recording from the select channel of the coresponding patient. The horizontal blue line indicates the seizure as identifed by VEM. The bottommost panel is the plot of the wavelet coefficients for the phase frequencies 0.5–10 Hz. Higher wavelet power is shown in red while lower power is in blue, scaled according to the color bar on the right. The middle panels show MI values in a 5 second window (indicated by the red horizontal lines) before the seizure, at seizure onset, during the seizure, at seizure termination, and after the seizure, respectively. The frequencies exhibiting strongest modulation are illustrated above. For all three patients the phase frequencies with strongest modulation were < 3 Hz. Note, the third MI panel for patient 1 has the full range of phase frequencies because of the transition into the theta rhythm during the seizure episode. For patients 1 and 2 the amplitude frequencies with strongest modulation were ≤ 150 Hz while for patient 3 they were 200–450 Hz. Stronger modulation is shown in red while weaker modulation is in blue, scaled according to the color bars are on the right of the last MI panel.

IV. Discussion

The emergence of delta-HFO modulation was found to occur at seizure onset and termination for all seven seizures obtained from these three patients, with the exception of the onset of the seizures from patient 1 wherein delta modulated the 40 Hz rhythm rather than frequencies of 80 Hz and higher. The relative strength of this delta modulation appears to be a reflection of the activity of the dominant lower frequencies observed in the wavelet coefficients. Although the activity within the seizure of each patient differs across patients, delta modulation at onset and termination of the seizure does not appear to be a patient-specific phenomenon. However, the specific HFO rhythm (i.e., ripple: 80–200 Hz, fast ripple: > 200–450 Hz) being modulated by it does seem to vary between patients. These different rhythms may be a reflection of the different cognitive states the patients are in. Previous studies have found that the sleep stage of the patient has an effect on the properties of the HFOs being recorded [12, 13]. Specifically, HFOs are fastest during nonREM sleep in comparison to both REM sleep and wakefulness. The seizures of patients 2 and 3 in this study were recorded during sleep whereas those of patient 1 were recorded during wakefulness. This may be one explanation as to why delta modulated the 40 Hz rhythm at seizure onset for patient 1 but the ripple and fast ripple rhythms for patient 2 and 3, respectively. Moreover, the difference between delta modulating the ripples and fast ripples for patients 2 and 3 suggest that these two patients were in different stages of the sleep cycle. Bagshaw *et al.* [12] also found that the spatial specificity of the fast ripples was affected by sleep stage and thus suggest that HFOs recorded during nonREM sleep may be more indicative of a seizure onset zone (SOZ) than those recorded during REM or wakefulness.

Several studies have shown that HFOs are more prevalent in the SOZ [14, 15] and are thus highly dependent on the spatial component of the recording. No attempts in this work were made to identify the SOZ nor are there any claims that the selected channels for this analysis were the optimal choice for observing the properties of HFOs. However, this preliminary analysis was able to capture one view of these delta-modulated HFOs in the selected channels. Further investigations into how this modulation changes not just in time but also in space across the various channels in the grid are likely to reveal ROIs that were not highlighted by the initial aWPC.

This notion of seizure onset and termination having similar dynamics has also been shown in rodents [16]. Seizure-like events (SLE) recorded from rodent hippocampal tissue were modeled as Markov processes – specifically, as hidden Markov models. Such models were able to capture multiple SLE states. Of particular interest is the first of these multiple states, which the network entered only on two instances – SLE onset and termination. This is not to say that the states preceding and immediately following a seizure or SLE are the same. On the contrary, this same rodent study found that the preSLE and postSLE states are indeed different. Rather, this study suggests that the hyperexcitable network of an epileptic brain first returns to the same state it was in at the beginning of a seizure before transitioning into a postictal state.

V. Conclusion

This study investigated the emergence of delta-modulated HFOs during seizure episodes of patients with intractable TLE. The strength of this modulation increases at seizure onset and termination regardless of the dynamics present within the seizure episode itself. Further studies investigating how this modulation changes in space across the iEEG grid in addition to the temporal changes explored in this study will be able to highlight the strength of this phenomenon as a potential iEEG-based biomarker for seizure state classification.

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