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Synchrony of High Frequency Oscillations in the Human Epileptic Brain

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Abstract— **We have applied wavelet phase coherence (WPC) to human iEEG data to characterize the spatial and temporal interactions of high frequency oscillations (HFOs; >80 Hz). Quantitative analyses were performed on iEEG segments from four patients with extratemporal lobe epilepsy. Interelectrode synchrony was measured using WPC before, during and after seizure activity. The WPC profiles of HFOs were able to elucidate the seizure from non-seizure state in all four patients and for all seizures studied (n=10). HFO synchrony was consistently transient and of weak to moderate strength during non-seizure activity, while weak to very strong coherence, of prolonged duration, was observed during seizures. Several studies have suggested that HFOs may have a significant role in the process of epileptogenesis and seizure genesis. As epileptic seizures result from disturbances in the regular electrical activity present in given areas of the brain, studying the interactions between fast brain waves, recorded simultaneously and from many different brain regions, may provide more information of which brain areas are interacting during ictal and interictal activity.**

I. Introduction

With the availability of improved recording techniques, very fast activities have become a new avenue of research in the area of seizure genesis. Initially identified in animals [1], high frequency oscillations (HFOs; >80 Hz) have since been successfully recorded in epileptic patients [2-4]. Recent studies have identified ictal and interictal HFOs as possible epileptogenic biomarkers. HFOs have been shown to arise in brain areas generating seizures [5, 6]. Similarly, Jirsch et al. [4] have demonstrated a focal increase of ictal HFOs in seizure-related regions of interest (ROI). Furthermore, new studies have demonstrated a correlation between the removal of areas with ictal HFO increases and a good post-surgical outcome [7-11]. However, there is still much to learn about these fast brain waves and their potential role in epileptogenesis, as it appears that spectral frequency alone cannot resolve physiological from pathological HFOs [12]. Here, we have studied HFO synchrony, analyzing intracranial subdural EEG grids in four patients with extratemporal lobe epilepsy.

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II. Patient Selection and Data Acquisition

Studies were conducted by the Thailand Comprehensive Epilepsy Program, Phramongkutklao Hospital (Bangkok, Thailand). iEEG data were collected from four patients with extratemporal lobe epilepsy, undergoing presurgical evaluation for epilepsy surgery. All patients underwent surgery for the placement of intracranial grids, arranged in a 64 contact (8x8) grid pattern (PMT, Chanhassen, MN, U.S.A.). All recordings were sampled at 2000 Hz (Stellate, Montreal, QC, Canada). The recordings were referenced to an electrode located at the forehead or behind the ears, but subsequently arranged offline in a bipolar arrangement in order to diminish artifacts. The bipolar arrangement consisted of taking the difference between pairs of neighboring electrodes, thereby reducing the number of electrodes for analysis to 32. Electrical noise, 50 Hz and harmonics, were removed using FIR notch filtering. All analyses were performed using MATLAB (The MathWorks, Natick, MA, U.S.A.).

III. Algorithms

Quantitative analysis was performed on iEEG recordings from all four patients. Interelectrode phase synchrony was measured using WPC, which was implemented in MATLAB (The MathWorks, Natick, MA).

A. Wavelet Phase Coherence

Phase synchrony involves the estimation of the instantaneous phases of electrical brain signals followed by a statistical method for quantifying the degree of phase locking. The phases of the original real valued signals may be transformed into complex-valued signals using auxiliary functions such as the Hilbert transform [13] or by convolution with a complex wavelet [14].

WPC is performed around a chosen frequency value, around which a frequency range is defined. This is repeated for all frequency values of interest until the entire spectrum under investigation has been covered (i.e. 1-400 Hz). The phases of the signals are obtained from the coefficients of their wavelet transform at the frequency of interest. The coefficients result from the convolution of the raw signals with a scaled Morlet wavelet whose center frequency is in the centre of the band of interest. At each time t and frequency f, the result of the convolution is a complex

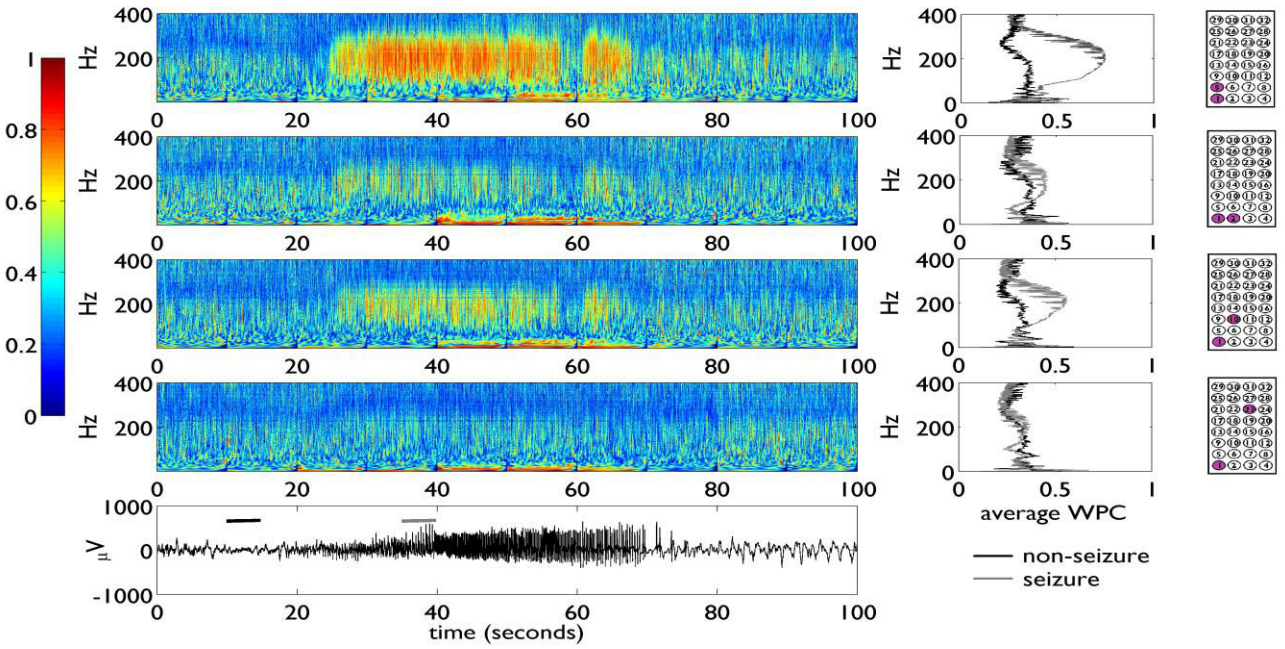

Figure 1. Wavelet phase coherence (WPC) from 1-400 Hz for four different electrode (E) pairings. WPC profiles for pairings E1-E5, E1-E2, E1-E10and E1-E23 from patient 1. Location of electrodes on patient grid are indicated to the right. The strength of WPC differs between electrode pairings across the frequency range shown. WPC of E1-E5, at higher frequencies, is stronger than that of E1-E2, even though both pairings are at close distances. Farther distances between electrode pairs does not always imply weaker WPC. WPC of E1-E23 is the weakest amongst all pairings shown, yet WPC of E1-E10, at higher frequencies, is stronger than that of E1-E2. Averaged WPC plots over 5 second durations are to the right of each plot. The temporal locations of the two segments shown are indicated by lines over a representative iEEG trace: non-seizure (black), seizure (gray). Note that WPC profiles for higher frequencies (i.e. 80-400) varied across different electrode pairings on the grid.

number $A(t,f)e^{i\phi(t,f)}$, where A is the amplitude and ϕ the phase of the signal. The phase difference of two signals (x_a and x_b) at a phase locking ratio of 1:1, for a given frequency is given by:

$$\varphi_{1,1}(t) = \phi_{x_a}(t) - \phi_{x_b}(t) \quad (1)$$

Next, the relative phase coherence between two signals for a given frequency band centered at frequency f and time segment centered at time $t=t_k$, and for sampling period Δt is obtained as follows:

$$\rho(f,t_k) = \left|\langle exp\left(i\emptyset_{1,1}(f,t_k)\right)\rangle\right| \quad (2)$$

$$= \left|\frac{1}{(N+1)}\right| \sum_{j=k-N/2}^{k+N/2} exp\left(i\emptyset_{1,1}(f,j\Delta t)\right)$$

The relative phase coherence varies between 0 (independent signals) and 1 (constant phase-lag between two signals). For our analysis, 13 iEEG segments from four patients were evaluated by WPC (mean duration of each segment: four minutes). Ten segments were comprised of a seizure episode accompanied by non-seizure activity (at least two seizures were included for each patient). Three segments were comprised of interictal activity. WPC was applied to every possible combination of electrode contacts from the implanted subdural grids. We calculated the WPC of frequency bands between 1-400 Hz with a frequency resolution of 1 Hz. A moving window of (1/f)*10 second duration was applied to each iEEG segment, where f is equal to the current frequency of interest. Each electrode pairing thus resulted in a WPC matrix ranging from 1-400Hz at a resolution of 1 Hz across time. To obtain average WPC profiles, these matrices were averaged across time and frequency for the indicated frequency ranges. Further details of phase synchronization can be found in Mormann et al. [15].

IV. RESULTS

The WPC profiles of fast activities showed minimal variations over time and space during non-seizure episodes. HFO (80-400 Hz) synchrony was consistently transient and of weak to moderate strength during non-seizure activity, for all electrode pairs. In contrast, weak to very strong coherence was observed in activities > 80 Hz during seizures (see Fig. 1). In Fig. 1, HFO (100-300Hz) WPC values for E1-E5 ranged from 0.20-0.38 and 0.43-0.75 for the marked non-seizure (black bar) and seizure (gray bar) segments respectively. Furthermore, WPC profiles were spatially heterogeneous during seizures. This trend is visible in Fig. 1, which includes the WPC profiles of four electrode pairings

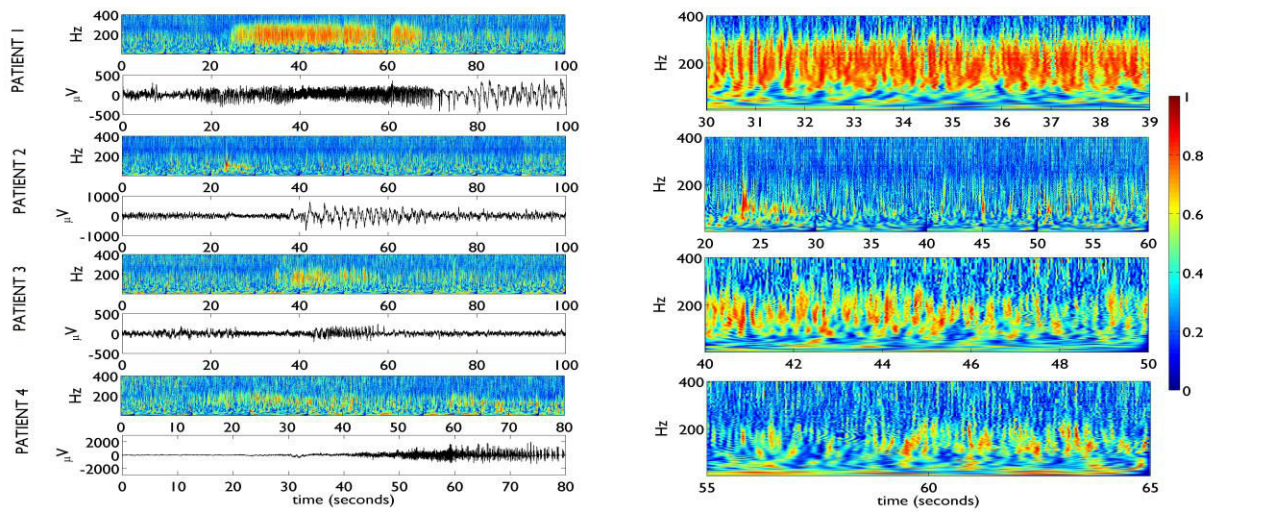

Figure 2. Strong coherence is present in the 80-350 Hz frequency range during seizures. WPC plots for all patients. Strong WPC is visible in the 80-350 Hz frequency range during a seizure for patient 1. Strong WPC is visible in the 80-180 Hz frequency range during a seizure for patient 2. Strong WPC is visible in the 80-300 Hz frequency range during a seizure for patient 3. Strong WPC is visible in the 80-250 Hz frequency range during a seizure for patient 4. The iEEG activity recorded from one of the electrodes in each pairing, and corresponding to the WPC plots are shown below each WPC plot of the left column. WPC seizure segments are expanded in the right column for all patients.

from the same patient. The WPC of electrodes 1 and 5 (E1-E5), at higher frequencies, was stronger than that of E1-E2, even though both pairings are separated by a similar distance. Farther distances between electrode pairs did not always result in weaker WPC. The WPC of E1-E23 was the weakest amongst all pairings shown, yet WPC of E1-E10, at higher frequencies, was stronger than that of E1-E2. In studying all possible electrode pairings for each patient, it became apparent that the strength of WPC was not dependent on just the distance between the electrode pairing, but whether the electrodes fell within the section of the grid later determined to possess the strongest HFO synchrony.

All four patients exhibited this similar trend of HFO synchrony: stronger synchrony in activity > 80 Hz during seizures and weaker HFO coherence during non-seizure segments. One electrode pairing from each patient is shown in Fig. 2. The WPC profiles of the electrode pairings shown here possessed stronger profiles compared to other pairings on the grid. Strong HFO synchrony was visible in activities > 80 Hz in all patients, however; the range of frequencies varied across patients. More specifically, strong WPC appeared during seizures in the 80-350 Hz band for patient 1, the 80-180 Hz band for patient 2, the 80-300 Hz band for patient 3 and the 80-250 Hz band for patient 4.

Average WPC (aWPC) matrices for HFOs were computed for all four patients over seizure and non-seizure segments. For aWPC matrices, an averaging over all windows and frequencies-in a given segment-and for each electrode pairing, was performed. To isolate HFO activity, the averaging was completed using only the high frequency bands. An example of such a matrix is shown in Fig. 3. The seizure matrix features regions of high synchronization, which are not present during non-seizure activity. The locations of strong ictal synchrony are shaded in green on the corresponding patient grids located below. Electrode pairings with synchrony values greater than the indicated threshold are shaded. Average WPC was calculated over the frequency ranges possessing strong WPC values: 80-350 Hz for patient 1 in Fig. 3.

V. DISCUSSION

Here, we have studied the synchrony of HFOs, as the pathological locking nature of seizure discharges readily observed in EEG recordings indicates a disturbance of the regular workings of brain rhythms. In our analysis of HFO coherence, it was observed that the WPC technique was able to elucidate the seizure from non-seizure state. HFO coherence was consistently transient and of weak to moderate strength during non-seizure activity. Weak to strong coherence, of prolonged duration, was observed in HFO activity during seizures. Furthermore, synchrony during ictal events was not spatially homogenous, and pairings which were strongly cohered showed a preference that was not always indicative of physical separation distance on the electrode grid. Thus, the WPC technique appears able to identify seizure events, as well as provide an indication of the degree of interaction of fast activities in different brain areas during ictal episodes. As a result, it is possible to observe the spatial relationship between areas of high synchronization with seizure-related ROIs from the aWPC generated matrices.

In studying WPC pairings across patients it was observed that HFO synchrony varied in bandwidth across electrode sites as well as across patients. It has been suggested that faster neuronal activities are generated by the hippocampus, while neocortical structures tend to generate slower HFOs (i.e. 80-250 Hz) [6]. Hence, it is possible that the generated

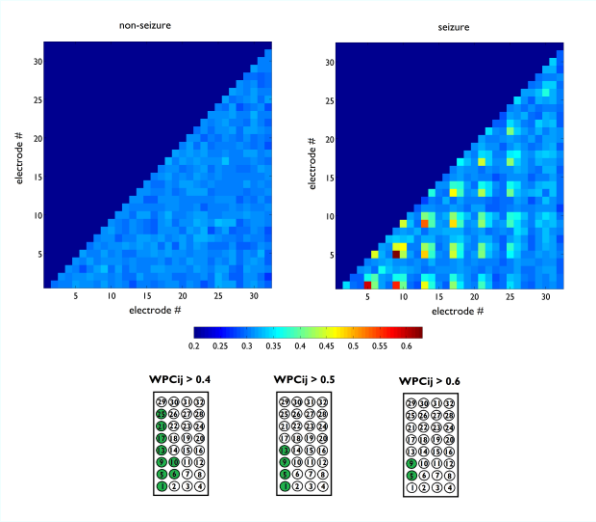

Figure 3. Average wavelet phase coherence (aWPC) matrices of HFO activity. Time and frequency averaged WPC matrices extracted from non-seizure and seizure segment for patient 1. Seizure matrices reveal areas of high synchronization, with the strongest coherence present between electrodes 5 and 9. The locations of strong synchrony are shown in green on the corresponding patient grid (bottom). Electrode pairings with aWPC higher than the indicated threshold are shaded. Average WPC was calculated over the frequency range: 80-350 Hz.

coherence frequency profiles are indicative of the underlying network dynamics.

In the human epileptic brain, several groups have studied the presence of HFOs and their spectral power changes as possible classifiers of the ictal state, as well as possible electrophysiological identifiers of seizure-related ROIs [4, 6, 16]. Jacobs et al. [6] have demonstrated that seizures originate from brain structures where the highest rates of HFOs are found. Moreover, several groups have recently demonstrated that the surgical removal of regions generating ictal HFO power increases, correlate with good seizure-free post-surgical outcome [7-11]. However, problems yet linger in the concrete identification of pathological HFOs. It has been observed that HFOs do not appear limited to the seizure-related ROIs but extend beyond. Furthermore, many studies have implemented HFO rates to distinguish epileptogenic regions; yet, it is not possible to define an absolute threshold rate, as they can be changed by such things as sleep or medication, and appear to be brain region and/or patient specific [16]. As such, additional characterization of HFO activity may complement these present techniques, as well as yield further insights into the workings of fast oscillations in the epileptic brain.

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