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Frequency Interactions in Human Epileptic Brain

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***Abstract*—We have used two algorithms, wavelet phase coherence (WPC) and modulation index (MI) analysis to study frequency interactions in the human epileptic brain. Quantitative analyses were performed on intracranial electroencephalographic (iEEG) segments from three patients with neocortical epilepsy. Interelectrode coherence was measured using WPC and intraelectrode frequency interactions were analyzed using MI. WPC was performed on electrode pairings and the temporal evolution of phase couplings in the following frequency ranges: 1-4Hz, 4-8Hz, 8-13Hz, 13-30Hz and 30-100Hz was studied. WPC was strongest in the 1-4Hz frequency range during both seizure and non-seizure activities; however, WPC values varied minimally between electrode pairings. The 13-30Hz band showed the lowest WPC values during seizure activity. MI analysis yielded two prominent patterns of frequency-specific activity, during seizure and non-seizure activities, which were present across all patients.**

I. Introduction

NEURAL electrical oscillations have been linked to and proposed to play a role in various physiological processes. Several studies have begun to correlate the oscillatory activity of the brain with such cognitive processes as memory, attention and consciousness [1],[2]. In the pathological brain, neural rhythms similarly remain a strong focus as abnormal oscillatory patterns have been observed for several disorders, including epilepsy, Parkinson's disease and schizophrenia [3],[4]. As oscillatory processes involve the large scale integration of distributed neuronal populations, the coupling and binding of various information-processing areas is required. As such, there is a general interest in studying the integration of neural activity by examining frequency interactions between signals. These interactions may encompass the coupling between amplitude envelopes, the coupling of phases as well as amplitude-phase coupling. Here, we have focused on the second and third methods of coupling to study frequency interactions in human epileptic brain. We have applied wavelet phase coherence (WPC) [5] and modulation index (MI) [1] analyses to study frequency associations between multichannel intracranial electroencephalography (iEEG) recordings, encompassing seizure and non-seizure data segments from three patients with epilepsy.

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II. Patient Selection and Data Acquisition

Data were collected from patients (n=3) undergoing pre-surgical evaluation of drug resistant neocortical epilepsy. Electrode strips, each possessing between 4-6 contacts were implanted subdurally in areas determined clinically to encompass seizure active zones. The data for Patient A included a total of 25 electrodes and 3 seizures, patient B 38 electrodes and 2 seizures and patient C 80 electrodes and 4 seizures. For each patient, all electrodes were referenced to an electrode located just below the scalp. Data for patients A and C were sampled at 250 Hz and for patient B at 500 Hz. 60 Hz noise and harmonics were removed using FIR notch filtering. All analyses were performed using Matlab (The MathWorks, Natick, MA).

III. Algorithms

Quantitative analysis was performed on iEEG recordings from all three patients. Interelectrode phase coherence was measured using WPC and intraelectrode frequency interactions were measured using MI analysis. Both algorithms were implemented in Matlab (The MathWorks, Natick, MA).

A. Wavelet Phase Coherence

Phase coherence involves the estimation of the instantaneous phases of electrical brain signals followed by a statistical method for quantifying the degree of phase locking. The original real valued signals may be transformed into complex-valued signals via auxiliary functions such as the Hilbert transform [6] or by convolution with a complex wavelet [7].

WPC is performed around a chosen frequency value, and a frequency range is defined around this chosen value. The process is repeated for all frequency values of interest until the entire portion of the spectrum under investigation has been covered (i.e. 1-100 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. Here, we have separated the raw signals into bands ranging from 1 - 100 Hz, in 1 Hz steps with 1Hz bandwidth, using the complex Morlet wavelet. At each time t and

frequency f, the result of the convolution is a complex 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:

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

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

$$\rho(f,t_k) = \left|\left\langle \exp(i\varphi_{1,1}(f,t_k))\right\rangle\right| = \frac{1}{(N+1)}\sum_{j=k-N/2}^{k+N/2}\exp(i\varphi_{1,1}(f,j\Delta t)) \qquad (2)$$

The relative phase coherence varies between 0 (independent signals) and 1 (constant phase-lag between two signals). WPC between electrode pairs was analyzed using a moving window of 1.0 s duration. For each patient, WPC was computed for all electrode pairs, for every consecutive window over the entire segment of interest. Pairings were chosen between electrodes located on the same strip (i.e. electrodes 1-4 on a single strip would result in the following pairings: (E1,E2), (E1,E3), (E1,E4), (E2,E3), (E2,E4) and (E3,E4). Each pairing thus resulted in a WPC matrix ranging from 1-100Hz at a resolution of 1 Hz across time. These matrices were then averaged across frequency, for the following physiological frequency ranges: 1-4Hz, 4-8Hz, 8-13Hz, 13-30 Hz and 30-100Hz. All electrode pairings, for the frequency ranges indicated above were combined and plotted to show the temporal evolution of the phase coupling between all electrode pairings (see figure 1). Further details of phase synchronization can be found in Mormann et al. [5].

B. Modulation Index

MI involves the construction of a composite complex-valued signal, created from the combination of the amplitude time series of one frequency with the phase time series of a second frequency:

$$z(t) = A_{f_1}(t)e^{i\phi_{f_2}(t)} \qquad (3)$$

where $f_1$represents the frequency of the amplitude time series and f_2 the frequency of the phase time series signal. Here we have chosen f_1 within the 8-100 Hz range and f_2 within the 1-39 Hz range (where $f_2 < f_1$), in 1Hz steps with a 1 Hz resolution, within the same electrode. The iEEG signals were first filtered at the frequency ranges of interest using FIR bandpass filters. The Hilbert transform was then applied to obtain the time series of the phases and the amplitude envelopes and the composite time series constructed from the combination of the phase and amplitude time series'. The mean of *z(t)*, (M), provides a measure of coupling between the two frequencies of interest. Further details on the calculation of M, and our implementation of the modulation index, which is based on the Matlab code provided in

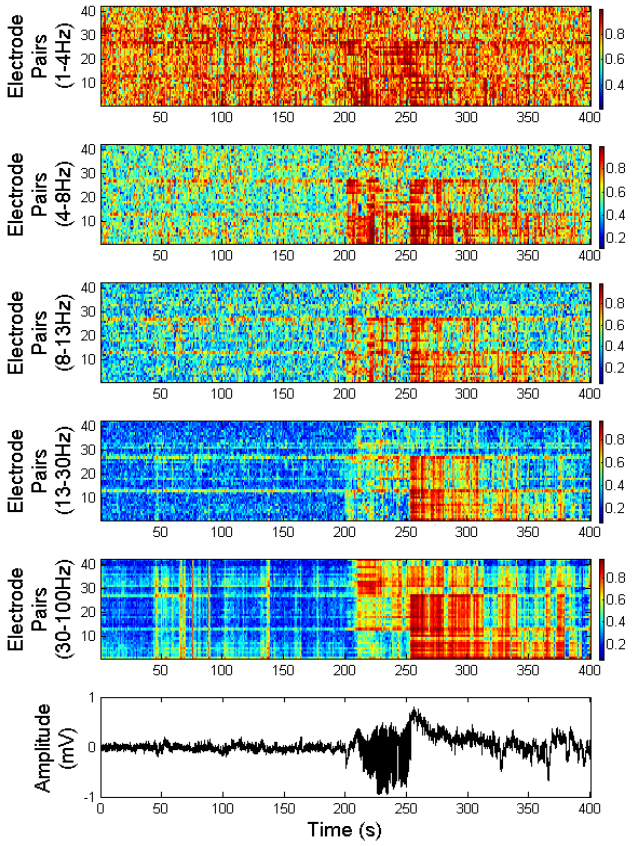

Figure 1. WPC electrode pairing profile for patient A. WPC electrode pairing profiles were created by averaging the WPC time series' across frequency, for the following physiological frequency ranges: 1-4Hz, 4-8Hz, 8-13Hz, 13-30 Hz and 30-100Hz. The distribution yields the temporal evolution of coupling between electrode pairings for the frequency ranges indicated.

Canolty et al., can be found in [1]. The MI was applied to all electrodes for all three patients using a moving window of 10.0s duration.

IV. Results

To study frequency interactions during seizure and non-seizure activities, WPC profiles for given frequency bands and electrode pairings were plotted, yielding the temporal evolution of phase couplings in the following frequency ranges: 1-4Hz, 4-8Hz, 8-13Hz, 13-30Hz and 30-100Hz. Figure 1 depicts the WPC electrode pairing profile for patient A. One iEEG channel is shown at the bottom for illustrative purposes. Overall, WPC values were strongest in the 1-4Hz frequency range during seizure and non-seizure activities, however, WPC values varied minimally between electrode pairings. Furthermore, the seizure episode is not readily discernable. This observation was consistent across all three patients.

Visual analysis of the distributions for all patients illustrated stronger WPC values in the non-seizure region for the lower frequency bands (i.e. 4-8Hz and 8-13 Hz) and weaker WPC values in the non-seizure region for the higher frequency ranges (13-30 Hz and 30-100 Hz). During seizure

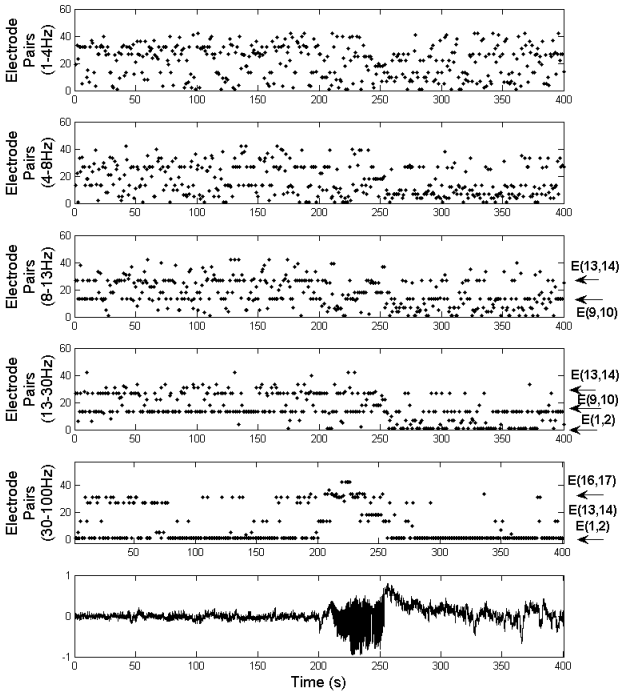

Figure 2. The maximum WPC time series was obtained for each frequency distribution for patient 1. For each time instant t, the max WPC was identified as well as its corresponding electrode pair. Max WPC varied spatially in the 1-4Hz range; no dominant electrode pairing was observed. All other frequency ranges identified at least one or more highly coupled electrode pairing (indicated to the right of each plot).

activities, high WPC values were observed across all frequency bands; however at the peak of seizure activity (i.e. 210-255s in figure 1), the 13-30Hz band consistently possessed the lowest WPC values.

The WPC profile for frequency ranges < 30 Hz possess similar distributions (i.e. similar strong/red zones and weak/blue zones), whereas the highest frequency band possesses the most distinct profile. Furthermore, all frequency bands possess horizontal 'bars' (during seizure and non-seizure segments) corresponding to strong phase locking in select electrode pairs, whereas the 30-100 Hz range alone possesses vertical 'bars', in the non-seizure segments, indicating strong coupling across all pairings at given time instances preceding the seizure.

The maximum WPC time series was obtained for the WPC electrode pairing distributions for patient 1 from figure 1. For each time instant t, the max WPC was identified as well as its corresponding electrode pair (see figure 2). Max WPC varied in the 1-4Hz range pairings; no dominant electrode pairings were observed. All other frequency ranges identified at least one or more strongly coupled electrode pairing (indicated by an arrow to the right of each plot, along with the corresponding electrode pair). Most prominent are the max WPC distributions for the 13-30 Hz and 30-100 Hz frequency ranges. For patient A, in the 13-30 Hz plot, the max WPC switches to a new electrode pairing towards the end of the peak seizure activity. In the 30-100 Hz range there

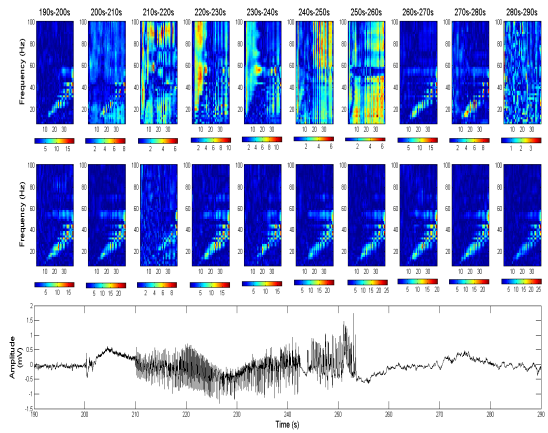

Figure 3. MI for channels 3 and 15 for patient A (seizure #1). Two prominent patterns of activity are discernable across all patient seizures. A low frequency-phase (3-10Hz), high- frequency amplitude (20-100Hz) coupling and a diagonal 'self-coupling' pattern in the 10-39 Hz frequency range. Frequency in Hz is along the x and y axes.

is a change in max WPC at the onset and for the duration of peak seizure activity; however max WPC returns to the same channel pairings following the end of the peak seizure activity.

To study cross-frequency couplings during seizure and non-seizure segments, the MI was applied to all electrodes. Two prominent patterns of activity were discernable across all patient seizures. A low frequency-phase (3-10Hz), high-frequency amplitude (LFP-HFA) (20-100Hz) coupling was observed only during seizure activities and a diagonal coupling pattern in the 10-39 Hz frequency range (see figure 3) was observed during both seizure and non-seizure activities. The LFP-HFA pattern was only observed in select electrodes, whereas the diagonal coupling pattern was visible in all electrodes during non-seizure segments and in select electrodes during seizure activities.

The MI profiles for max electrode pairings identified in figure 2 are plotted in figure 4. All pairings were strongly phase-locked across all seizures (n=3) studied for patient A. Three of the four sets of electrode pairings demonstrated LFP-HFA patterns of activity during seizure segments.

V. Discussion

Electrical rhythms of the brain are being closely examined in relation to epilepsy, as the pathological locking of seizure discharges indicates a disturbance in the integration of cortical activities. We have applied wavelet phase coherence and modulation index analyses to study phase associations and cross-frequency couplings between channels of multisite iEEG recordings from patients with neocortical epilepsy.

Several studies have applied WPC to seizure activities, demonstrating a decrease in long range synchronization as compared with controls [8-11], as well as a decrease in synchronization at seizure onset [9]. Given that the majority of these studies have explored the measure of mean phase coherence, the purpose of this paper is to study this analysis

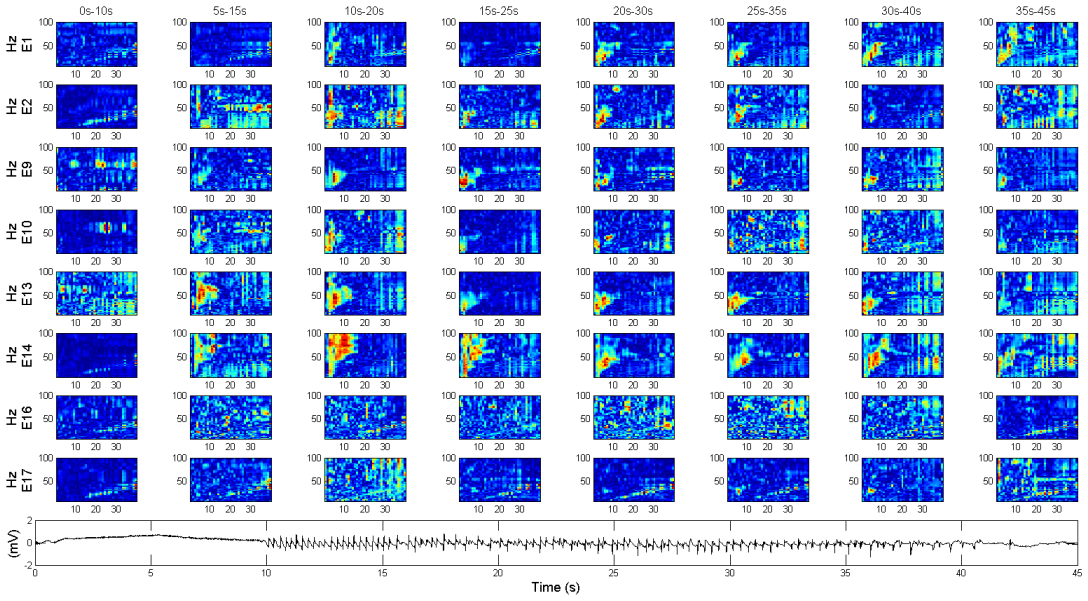

Figure 4. MI profiles for electrodes possessing strongest WPC values. Electrodes 1, 2, 9, 10, 13, 14, 16, 17 for patient A and seizure #2 are shown. A low frequency-phase (3-10Hz), high- frequency amplitude (20-100Hz) coupling is present in 6 of the 8 electrodes. Frequency in Hz is along the x and y axes.

index in a temporal context, across multisite recordings, to identify which frequency couplings are active/inactive at various times during a seizure and the manner in which their locking is spatially distributed.

As frequency coding is an intrinsic neural property, the combination of multiple frequency analysis techniques applied in conjuncture may provide further insights into the spread of epileptic activity by revealing distinctive patterns of frequency-specific phase coherence and/or frequency coupling associated with the pathological oscillations observed in the epileptic brain, at multiple electrode sites.

Gamma activity in the brain (30-100 Hz) has been proposed as a candidate mechanism for connecting or 'binding' spatially distributed brain activities. Here, we have shown that the 30-100 Hz frequency range possessed its own distinct phase locking profile, compared to those of the lower frequency ranges analyzed. Furthermore, MI analysis revealed a low-frequency phase (3-10Hz), high frequency amplitude (20-100Hz) coupling in most electrodes possessing strong WPC values. Theta and gamma activity are both prominent coherent rhythms observed in healthy hippocampi in both human and animal models. Gamma often co-occurs and is temporally internested with the theta rhythm with several studies having indicated a strong role for gamma-band oscillations and gamma-theta coupling in learning and memory processes [1],[4]. Gamma activity dysfunction has been associated with several mental disorders including epilepsy [4],[12]. The further study of these rhythms, their phase and coupling behaviours, may provide additional insights into the initiation, maintenance and spread of epileptic activity.

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