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Dynamical Analysis of Seizure in Epileptic Brain: a Dynamic Phase-Amplitude Coupling Estimation Approach

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***Abstract*—Cross-frequency coupling in general and phase-amplitude coupling (PAC) as a particular form of it, provides an opportunity to investigate the complex interactions between neural oscillations in the human brain and neurological disorders such as epilepsy. Using PAC detection methods on temporal sliding windows, we developed a map of dynamic PAC evolution to investigate the spatiotemporal changes occurring during ictal transitions in a patient with intractable mesial temporal lobe epilepsy. The map is built by computing the modulation index between the amplitude of high frequency oscillations and the phase of lower frequency rhythms from the intracranial stereoelectroencephalography recordings during seizure. Our preliminary results show early abnormal PAC changes occurring in the preictal state prior to the occurrence of clinical or visible electrographic seizure onset, and suggest that dynamic PAC measures may serve as a potential clinical technique for analyzing seizure dynamics.**

***Clinical Relevance*—Application of a dynamic temporal PAC map as a new tool may provide novel insights into the neurophysiology of epileptic seizure activity and its spatio-temporal dynamics.**

I. Introduction

Epilepsy represents a common disorder affecting 3.4 million people in the US and more than 50 million people worldwide [1]. Despite major pharmaceutical treatment advancements, approximately 30% of patients have intractable seizures refractory to antiepileptic drug (AED) treatment [2], [3]. Mesial temporal lobe epilepsy (TLE) is the most common form of epilepsy in adults [4] and represents the most common type of refractory partial epilepsy referred for surgery [5]. Although a landmark randomized clinical trial has shown that surgery is superior to prolonged medical therapy for patients with refractory TLE [6], seizures recur in 30% to 54% of patients after surgery [7].

Recurrent seizures caused by abnormal discharges of neurons with pathological network hypersynchrony seems to be a key feature of epilepsy even though there are different clinical manifestations [8]. The TLE pathophysiological substrate is often hippocampal sclerosis however, the fundamental neuronal mechanisms underlying the epileptogenic dynamics are not well elucidated. Previous studies have described an abnormal network synchronization with cellular and network hyperexcitability originating from the hippocampus and/or parahippocampal region [4], [9], [10]. In the same setting, it was demonstrated by using a cellularly detailed network computer model of the dentate gyrus that non-random interconnected granule cell hubs can cause a hyperexcitable, potentially seizure-prone network [8], [11]–[13]. Thus, recent evidence suggests the crucial role of brain wave synchronization in the pathophysiology of epilepsy highlighting the potential relevance of this feature as an indicator of epilepsy.

The oscillatory electrical activity of neurons serves a fundamental role in intra- and inter-network communication and the variability of the brain waves can be detected by analyzing different band characteristics such as the power of the different frequency bands as well as the interaction between the different bands via phase amplitude coupling (PAC) [14]. PAC investigates local and large-scale synchronization between cells and its relevance to human disease was previously portrayed in various neurological disorders including epilepsy [15]. Disruption of normal PAC patterns was described in epileptic human and rodent models where PAC was reported stronger in the pre-ictal and ictal periods as well as in the seizure onset zones [16]–[20]. This method has been used to study the abnormal synchronization occurring during seizure and has been related to post-surgical clinical outcomes [21].

In the current study, we aimed to extrapolate our work with dynamic PAC and investigate the electrophysiological changes occurring in the setting of intracranial stereoelectroencephalography (sEEG) recordings performed for seizure onset zone (SoZ) localization in the setting of intractable epilepsy.

II. Materials and Methods

The study was approved by the Johns Hopkins University Institutional Review Board and written informed consent was obtained from the subject.

*YS and DG equally contributed to the ideas and concepts discussed within this manuscript.

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A. Illustrative data

We analyzed SEEG recordings from one patient with intractable complex partial seizures undergoing invasive presurgical evaluation. The patient's case was discussed at the Johns Hopkins Multidisciplinary Epilepsy Conference and the electrode placement was performed with ROSA assisted neuro-navigation based on the surgical planning in order to target the anatomical structures believed to be involved in the seizure onset zone and propagation.

The hypothesized seizure onset zone was determined based on the seizure semiology, ictal and interictal electrophysiological patterns, imaging studies (MRI/PET) and neuropsychological evaluation. From a total of 8 depth electrodes implanted, we analyzed 2 Ad-Tech depth electrodes (5 mm contact spacing) recording the seizure onset zone, namely the anterior and posterior hippocampus. The localization of electrodes was confirmed with post-operative MRI and CT and 3D maps were performed as per previous publications (Figure 1). The image processing involved 3D reconstruction of the SEEG electrodes using post-surgical MRI and CT.

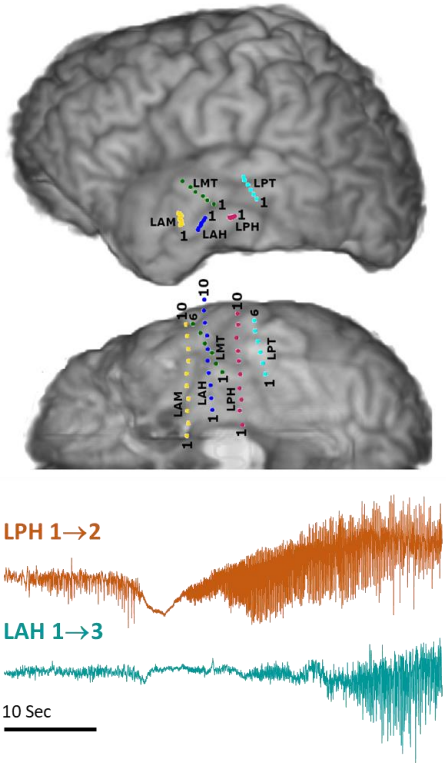

Figure 1. Illustration of the implanted electrodes from the sample subject rendered on a normalized cortical surface. The electrode contact coordinates were extracted from the post-op CT and transferred to the pre-op MRI coordinate system and then mapped to the 3D brain rendering. The lower panel illustrates the temporal pattern of recorded iSEEG signals from the hippocampus.

The intracranial stereoelectroencephalography (iSEEG) signals were acquired using the Nihon Kohden software sampled at 1000 Hz. The electrographic SoZ was identified by a board certified epileptologist (JK).

B. Dynamic modulation index.

To quantify high frequency power (gamma power) modulation by the phase of the low frequency oscillations (theta or beta), a dynamic modulation index (DMI) was used. DMI is defined based on a limited modulation index (MI) estimation [22],[23] which is summarized here. Let $X_{ECoG}(t)$ denote a segment of recorded ECoG signal extending from the presentation of the probe until the subject's response. In Step I, $X_{ECoG}(t)$ is decomposed into a low frequency band signal, $X_L(t)$, and a series of high frequency bands, $X_{iH}(t)\ i = 1, \dots, n$, with 10Hz steps. In Step II, the phase of $X_L(t)$ (denoted as $\psi_L(t)$) and amplitude envelope of $X_{iH}(t)\ i = 1, \dots, n$ (denoted as $A_{iH}(t)$) is obtained from the standard Hilbert transform of $X_L(t)$ and $X_{iH}(t)\ i = 1, \dots, n$ respectively. The two-dimensional signals $A_{iH}(t) \times \exp(\psi_L(t));\ i = 1, \dots, n,$ are then generated (Step III), which include the amplitude of the $X_{iH}(t);\ i = 1, \dots, n$ at each phase of the $X_L(t)$. The phase $\psi_L(t)$ is binned into N intervals, and the mean of $A_{iH}(t);\ i = 1, \dots, n$ over each phase bin is calculated (denoted as $< A_{1H} >_{\psi_L(t)}$ (j)) and normalized over all bins (Step IV). In Step V, the entropy measure $H_i, i = 1, \dots, n$ is calculated and in Step VI, and the MI is estimated by normalizing $H_i, i = 1, \dots, n$ to the maximum possible entropy value which is equal to log N. Finally, a vector is generated that summarizes the PAC signal in the high frequency interval with respect to the specific low frequency band. By having a sliding window which advances by specific steps, a dynamic representation of PAC is generated. Statistical control analysis using surrogate time series is used for investigating the accuracy of MI estimation (by keeping the original amplitude data and randomizing the phase information) [23],[24].

III. Results

We analyzed resting state pre-, post-ictal and ictal SEEG recordings from a patient with intractable complex partial epilepsy. The SEEG electrodes position with respect to anatomic structures are depicted in Figure 1 (upper panel). Contacts are numbered from the most deep to the most superficial electrodes (i.e. 1 represents the most deep or medial electrode). Examples of SEEG recordings including 120 sec pre-ictal, ictal and 120 sec post-ictal recordings during one seizure in the left posterior hippocampus (LPH) and left anterior hippocampus (LAH) are shown in Figure 1 (lower panel).

Standard spectrogram and power/frequency analysis of the same dataset are depicted in Figure 2. This demonstrates a clear change in both the power and frequency characteristics with the ictal onset. Figure 3 illustrates the results of PAC where we can visualize a similar pattern corresponding with the ictal onset. This is in keeping with previous publications showing an increase in PAC with ictal

onset. Subsequently, we computed for the same dataset the dPAC between the phase of the low frequency oscillations (theta) and the power of the high frequency (gamma) using the dynamic modulation index (DMI). Interestingly, using the dynamic PAC, we visualized a focal increase in the dPAC for both electrodes just prior to the electrographic ictal onset. (Figure 4).

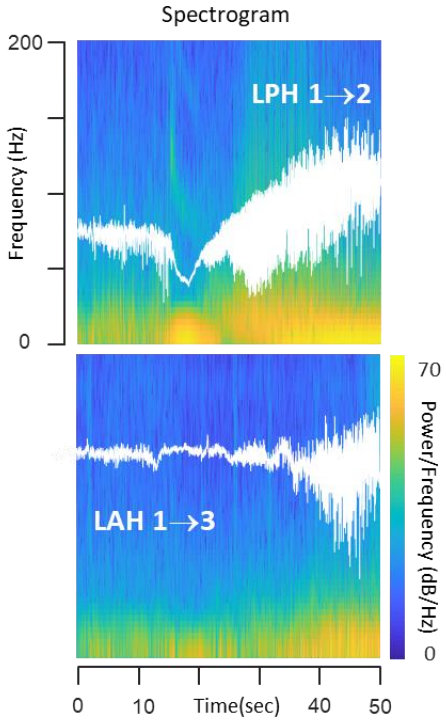

Figure 2. The spectrograms of the two sample waveforms are illustrated.

IV. Discussion

Epilepsy represents one of the most common neurological disorders and although for many patients, epilepsy can be treated pharmacologically or through surgery, for a substantial subset of patients it remains intractable. One of the most disabling features of epilepsy is its unpredictable nature and as such, deciphering the underlying mechanisms of seizure initiation represents a major field of research. Understanding the underlying mechanism of epilepsy and the process by which the brain state transitions to a seizure including the cellular and network mechanisms is crucial for enabling the development of new treatment strategies. Previous studies emphasized the importance of the spatiotemporal dynamics of the seizure development. Although seizures appear to initiate abruptly when analyzed at a macroscopic level, detailed analyses have shown the dynamic nature of seizure buildup with a transition from a physiological preictal state to the pathophysiological seizure through a preictal period with increased neuronal firing and hypersynchrony [25].

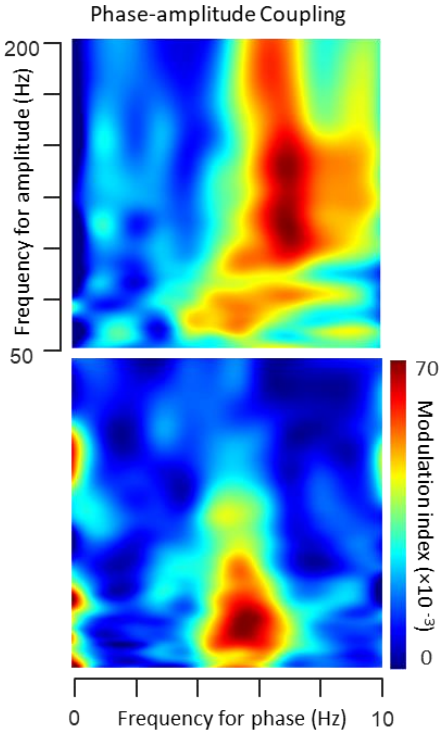

Figure 3. The level of the coupling quantified by the modulation index between the theta frequency phase and gamma frequency amplitude for the sample data recorded from hippocampus is shown.

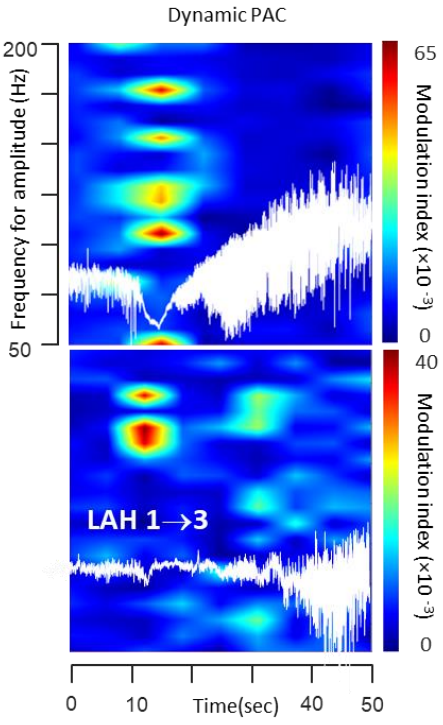

Figure 4. For the two sample iSEEG the dynamic PAC was computed over a 5s sliding window of 500ms using modulation index estimation.

Jiruska et al. showed that immediately preceding temporal lobe seizures, in the hippocampal CA1 region there is a preictal state characterized by a progressive increase in neuronal firing (mainly pyramidal cells) that is associated with reduction in system complexity and build-up of low-amplitude high-frequency activity (HFA- >100 Hz) [25]. The transition to seizure was characterized by a "rapid expansion and fusion of the neuronal populations responsible for HFA, leading to a single, massive, hypersynchronous cluster generating the high amplitude low- frequency activity of the seizure" [25]. As such, CA1 was found to have a pre-ictal low seizure threshold that makes it susceptible to endogenous perturbations that might provide the seizure trigger. In the same setting, Perucca et al. showed a widespread progressive increase in each frequency band activity from baseline to the preictal state suggesting that there might be a facilitating mechanism enabling a region to be susceptible for seizure generation[26]. Furthermore, an impaired balance of excitation and inhibition is thought to contribute to the network hyperexcitability and the appearance of hypersynchronous neuronal discharges responsible for generating spontaneous seizures [27].

For these reasons, oscillatory synchronization, particularly PAC, is a prime target for both understanding the pathophysiology of network disorders and for targeting by therapeutic intervention.

The current study presents, for the first time to our knowledge, the use of dynamic PAC to investigate the spatiotemporal changes occurring at the transition to seizure in a patient with intractable mesial temporal lobe epilepsy undergoing SEEG recordings. This pilot study revealed early PAC changes occurring in the preictal state prior to the occurrence of clinical or visible electrographic seizure onset. The dPAC could thus represent a potential novel epilepsy biomarker and target for novel treatments aiming to prevent clinical seizures via interruption at early electrographic stages.

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