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Temporal-spatial characteristics of phase-amplitude coupling in electrocorticogram for human temporal lobe epilepsy

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HIGHLIGHTS

- Phase-amplitude coupling (PAC) can provide relevant information for the lateralization and localization of epileptic foci.
- The “fall-max” pattern was found to be a reliable biomarker in the mid-seizure period.
- Strong PAC appeared mainly between δ, θ, and α oscillations and γ and ripple oscillations.

ABSTRACT

Objective: Neural activity of the epileptic human brain contains low- and high-frequency oscillations in different frequency bands, some of which have been used as reliable biomarkers of the epileptogenic brain areas. However, the relationship between the low- and high-frequency oscillations in different cortical areas during the period from pre-seizure to post-seizure has not been completely clarified.
Methods: We recorded electrocorticogram data from the temporal lobe and hippocampus of seven patients with temporal lobe epilepsy. The modulation index based on the Kullback-Leibler distance and the phase-amplitude coupling co-modulogram were adopted to quantify the coupling strength between the phase of low-frequency oscillations (0.2–10 Hz) and the amplitude of high-frequency oscillations (11–400 Hz) in different seizure epochs. The time-varying phase-amplitude modulogram was used to analyze the phase-amplitude coupling pattern during the entire period from pre-seizure to post-seizure in both the left and right temporal lobe and hippocampus. Channels with strong modulation index were compared with the seizure onset channels identified by the neurosurgeons and the resection channels in the clinical surgery.
Results: The phase-amplitude coupling strength (modulation index) increased significantly in the mid-seizure epoch and decrease significantly in seizure termination and post-seizure epochs ($p < 0.001$). The strong phase-amplitude-modulating low- and high-frequency oscillations in the mid-seizure epoch were mainly δ, θ, and α oscillations and γ and ripple oscillations, respectively. The phase-amplitude modulation and strength varied among channels and was asymmetrical in the left and right temporal cortex and hippocampus. The “fall-max” phase-amplitude modulation pattern, i.e., high-frequency amplitudes were largest in the low-frequency phase range $[-\pi, 0]$, which corresponded to the falling edges of low-frequency oscillations, appeared in the middle period of the seizures at epileptic focus channels. Channels with strong modulation index appeared on the corresponding left or right temporal cortex of surgical resection and overlapped with the clinical resection zones in all patients.
Conclusions: The “fall-max” pattern between the phase of low-frequency oscillation and amplitude of high-frequency oscillation that appeared in the middle period of the seizures is a reliable biomarker in

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epileptogenic cortical areas. The modulation index can be used as a good tool for lateralization and localization for the epileptic focus in patients with epilepsy.

Significance: Phase-amplitude coupling can provide meaningful reference for accurate resection of epileptogenic focus and provide insight into the underlying neural dynamics of the epileptic seizure in patients with temporal lobe epilepsy.

1. Introduction

Abnormal discharge of neurons in the epileptic human brain causes the specificity of the neural oscillations of the cerebral cortex. The low- and high-frequency neural oscillations of some frequency bands have been known as the essential biomarkers of epileptogenicity and epileptic seizure onset zones. The dynamic process of very low-frequency oscillations (LFOs) in the intracranial electroencephalographic recordings has been found to occur during the preictal state in patients with refractory epilepsy (Ren et al., 2011). Ictal infraslow activity and ictal high-frequency oscillations (HFOs) both represent the core of the tissue generating seizures in patients with epilepsy (Imamura et al., 2011; Kanazawa et al., 2015). Moreover, Crépon et al. used the semi-automatic detection procedure of wavelet decomposition to confirm the generation of interictal HFOs of over 200 Hz in medial and polar temporal lobes, which was regarded as a reliable marker of the seizure onset zone (Crépon et al., 2010). Resection of cortical areas generating fast ripples (>200 Hz) and ripples on a flat background activity has also been found to show a significant correlation with seizure-free outcome (Kerber et al., 2014). Moreover, temporal changes in ripples (100–250 Hz) and fast ripples (250–500 Hz) during different seizure periods have been found to vary greatly between individual patients with epilepsy (Pearce et al., 2013). These LFOs and HFOs that occur in patients with epilepsy have been considered potential biomarkers of epileptogenesis. However, they offered limited insight into the features of neural oscillations during the epileptic seizures because the complex neural activities in the epileptic cerebral cortex are constituted by simultaneous neural oscillations in different frequency bands.

The interactions between neural oscillations in different frequency bands, which are termed as cross-frequency coupling (CFC), play an important role in investigating the mechanisms of the communication and connectivity in neural networks. Phase-amplitude coupling (PAC), a form of CFC in which the phase of LFO modulates the amplitude of HFO, has become a rising concern in recent studies. Alvarado-Rojas et al. used cross-frequency PAC in ECoG of patients with partial epilepsy to predict the seizures (Alvarado-Rojas et al., 2011). CFC between the amplitude of pathological HFOs and the phase of θ and α rhythms was found to be significantly elevated in the seizure onset zone compared to non-epileptic regions in patients with partial epilepsy (Ibrahim et al., 2014). Moreover, Guirgis et al. adopted the measures of modulation index (*MI*) and eigenvalue decomposition to confirm that δ-modulated HFOs could provide more accurate localization of epileptogenic zones in patients with extratemporal lobe epilepsy (Guirgis et al., 2015a). Recently, *MI* was also used to determine the predictive accuracy of seizure onset sites and eloquent areas in children with focal epilepsy, which suggested that epileptogenic HFOs might be coupled with slow waves of 3–4 Hz more preferentially than slow waves of 0.5–1 Hz (Nonoda et al., 2016). In addition, PAC was estimated from the synchronization index for ECoG from patients with refractory temporal lobe epilepsy and accurately distinguished the ictal state from interictal state with strong coupling between the phase of β oscillation and the amplitude of high γ oscillation (Edakawa et al., 2016).

Previous studies concentrated more on the coupling strength, coupling frequency bands, or coupling areas of the brain between the phase of LFO and amplitude of HFO. However, the coupling patterns of phase-amplitude interaction in different brain areas during non-seizure and seizure periods remain unclear. Therefore, this study aimed to investigate whether PAC differs in different seizure periods and in what forms do the low-frequency phase and high-frequency amplitude couple. Moreover, we aimed to estimate whether PAC differs in the left and right temporal cortex and hippocampi of patients with temporal lobe epilepsy.

To address and better understand these issues, we collected the ECoG data from the left and right temporal cortex and hippocampi of seven patients with temporal lobe epilepsy. We adopted the *MI* based on the Kullback-Leibler distance (Tort et al., 2010), PAC comodulogram, and time-varying phase-amplitude modulogram (Mukamel et al., 2011) to explore the temporal-spatial characterization of PAC strength and patterns during the period from pre-seizure to post-seizure in both sides of the cortex (see Materials and methods for details).

2. Materials and methods

2.1. Data recordings and preprocessing

We obtained ECoG recordings from subdural strip electrodes implanted in seven patients. Six patients presented with suspected bilateral temporal lobe epilepsy, and one presented with right temporal lobe epilepsy. All patients provided written informed consent, and the study was approved by the ethics committees of Xuanwu Hospital (Patient A, B, C, and D) and Luhe Hospital (Patient E, F, and G). All seven patients had pathologically focal cortical dysplasia (FCD). The clinical characteristics of each patient are summarized in Table 1. The cortical electrode strip (2.5 mm diameter platinum electrodes positioned 10 mm apart center-to-center) and depth electrode strip (1.2 mm diameter platinum electrodes positioned 10 mm apart center-to-center) were implanted on the temporal lobes and hippocampi of each patient, respectively. All electrode strips were placed symmetrically on the left and right cerebral cortex, except for patient E. The strips of patient E were placed only on the right cerebral cortex. The spatial distribution of preoperative intracranial electrode strips of patient A is shown in Fig. 1A. The top panel shows the left and right views of cerebral cortex, while the bottom panel shows the top and upward views of cerebral cortex. We arranged all the electrode strips in a plane (Fig. 1B) to allow for easy observation.

ECoG signals were continuously recorded day and night for the preoperative assessment of all patients using a video-EEG monitoring system (PN-NET, Beijing Yunshen Technology, China). An electrode located far from the epileptic focus was used as the reference electrode. The sampling frequency of the ECoG data was 2048 Hz. The ECoG data were exported as European Data Format Plus (EDF+) files and imported into EEGLAB for changing the file format