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Interictal high-frequency oscillations generated by seizure onset and eloquent areas may be differentially coupled with different slow waves

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HIGHLIGHTS

- Interictal HFOs were noted in seizure-onset and sensorimotor–visual sites during sleep.
- Epileptogenic HFOs may be more preferentially coupled with slow waves of 3–4 Hz.
- Physiologic HFOs may be more preferentially coupled with slow waves of 0.5–1 Hz.

ABSTRACT

Objective: High-frequency oscillations (HFOs) can be spontaneously generated by seizure-onset and functionally-important areas. We determined if consideration of the spectral frequency bands of coupled slow-waves could distinguish between epileptogenic and physiological HFOs.
Methods: We studied a consecutive series of 13 children with focal epilepsy who underwent extraoperative electrocorticography. We measured the occurrence rate of HFOs during slow-wave sleep at each electrode site. We subsequently determined the performance of HFO rate for localization of seizure-onset sites and undesirable detection of nonepileptic sensorimotor–visual sites defined by neurostimulation. We likewise determined the predictive performance of modulation index: $MI_{(XHz)\&(YHz)}$, reflecting the strength of coupling between amplitude of $HFOs_{XHz}$ and phase of $slow\text{-}wave_{YHz}$. The predictive accuracy was quantified using the area under the curve (AUC) on receiver-operating characteristics analysis.
Results: Increase in HFO rate localized seizure-onset sites ($AUC \geqslant 0.72$; $p < 0.001$), but also undesirably detected nonepileptic sensorimotor–visual sites ($AUC \geqslant 0.58$; $p < 0.001$). Increase in $MI_{(HFOs)\&(3-4Hz)}$ also detected both seizure-onset ($AUC \geqslant 0.74$; $p < 0.001$) and nonepileptic sensorimotor–visual sites ($AUC \geqslant 0.59$; $p < 0.001$). Increase in subtraction-MI_{HFOs} [defined as subtraction of $MI_{(HFOs)\&(0.5-1Hz)}$ from $MI_{(HFOs)\&(3-4Hz)}$] localized seizure-onset sites ($AUC \geqslant 0.71$; $p < 0.001$), but rather avoided detection of nonepileptic sensorimotor–visual sites ($AUC \leqslant 0.42$; $p < 0.001$).
Conclusion: Our data suggest that epileptogenic HFOs may be coupled with $slow\text{-}wave_{3-4Hz}$ more preferentially than $slow\text{-}wave_{0.5-1Hz}$, whereas physiologic HFOs with $slow\text{-}wave_{0.5-1Hz}$ more preferentially than $slow\text{-}wave_{3-4Hz}$ during slow-wave sleep.
Significance: Further studies in larger samples are warranted to determine if consideration of the spectral frequency bands of slow-waves coupled with HFOs can positively contribute to presurgical evaluation of patients with focal epilepsy.

1. Introduction

Extraoperative electrocorticography (ECoG) is commonly utilized as a part of presurgical evaluation for patients with medically-uncontrolled focal seizures in a number of epilepsy

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centers. The ultimate purpose of extraoperative ECoG is localization of the epileptogenic zone of which surgical resection results in seizure control as well as delineation of the eloquent areas of which preservation minimizes the risk of postoperative functional deficits (Rosenow and Lüders, 2001). The gold-standard electrophysiological biomarkers for estimation of the epileptogenic zone include the seizure-onset zone involved in generation of habitual seizures, namely, the electrode site(s) initially showing the ictal ECoG discharges prior to habitual seizures (Asano et al., 2009). Conversely, significance of seizure-onset zones involved in non-habitual seizures is currently unknown (Kovac et al., 2014). A long period of extraoperative ECoG recording may be undesirably needed to capture habitual seizures, and some patients do not achieve seizure-freedom even after complete resection of the seizure-onset zone (Asano et al., 2009). Thus, investigators are currently looking for alternative biomarkers estimating the extent of the epileptogenic zone.

Promising candidate biomarkers include interictal high-frequency oscillations (HFOs) spontaneously and intermittently generated during resting periods (Jacobs et al., 2012; Zijlmans et al., 2012). Studies of both pediatric and adult populations reported that surgical failure was associated with a high rate of interictal HFOs generated by the non-resected tissues during non-REM sleep and under general anesthesia (Jacobs et al., 2010; Wu et al., 2010; Akiyama et al., 2011; van't Klooster et al., 2015). A large number of investigators independently reported that electrode sites frequently generating HFOs often turn out to be a part of the seizure-onset zones (Staba et al., 2002; Bagshaw et al., 2009; Crépon et al., 2010; Akiyama et al., 2011; Blanco et al., 2011; Gliske et al., 2016; Sakuraba et al., 2016). Sites showing $HFOs_{>80Hz}$ and $HFOs_{>250Hz}$ are often overlapped in space (Jacobs et al., 2011), but $HFOs_{>80Hz}$ are generated by larger brain regions (Zijlmans et al., 2012). Some studies suggested that the occurrence rate of $HFOs_{>250Hz}$ predicted the postoperative seizure outcome somewhat better than that of $HFOs_{>80Hz}$ (Akiyama et al., 2011; van't Klooster et al., 2015). Others suggested that $HFOs_{>80Hz}$ may be more useful than $HFOs_{>250Hz}$, which are difficult to detect in a substantial proportion of patients with neocortical epilepsy (Blanco et al., 2011; Wang et al., 2013).

Despite the efforts of many investigators, the clinical utility of interictal HFOs still remains uncertain (Jobst, 2013), particularly because HFOs are frequently generated by nonepileptic visual, somatosensory, motor, and auditory cortices during resting periods (Blanco et al., 2011; Fukushima et al., 2012; Nagasawa et al., 2012; Melani et al., 2013; Wang et al., 2013; Alkawadri et al., 2014; van't Klooster et al., 2015). The current recommendation is that one should not determine the resection margin solely based on the occurrence rate or spectral frequency band of interictal HFOs (Engel et al., 2009; Asano et al., 2013; Gliske et al., 2016). A method that can distinguish epileptogenic from physiologic HFOs in an automatic and efficient manner is highly desirable.

Our central hypothesis was that consideration of the spectral frequency band of slow-waves coupled with HFOs would improve the specificity of prediction of seizure-onset zone responsible for generation of habitual seizures. Our preliminary study of interictal ECoG during slow-wave sleep showed that HFOs in the nonepileptic occipital pole were strictly coupled with slow wave at 1 Hz and below, whereas HFOs in the seizure-onset zones coupled with slow wave at 3–4 Hz also (Nagasawa et al., 2012). Another group reported that both nonepileptic visual and sensorimotor areas can frequently generate interictal HFOs independent from interictal spike discharges (Wang et al., 2013). It is plausible that seizure-onset zone could be predicted by measuring *in situ* modulation index: $MI_{(HFOs)\&(slow\text{-}wave)}$, a measure that reflects the degree of stability of phase–amplitude coupling between HFO amplitude and slow-wave phase (Canolty et al., 2006). In theory, $MI_{(>XHz)\&(YHz)}$ is greater if a larger amplitude of $HFOs_{>XHz}$ are more consistently coupled with a phase of $slow\text{-}wave_{YHz}$. Here, we measured MI at all electrode sites during interictal state on the first evening of extraoperative ECoG recording, using an open source toolbox EEGLAB and its extension Phase–Amplitude Coupling Toolbox (PACT) that incorporates the algorithm and routines for measurement of MI (Miyakoshi et al., 2013).

The first aim of this study was to determine, using receiver operating characteristics (ROC) analysis, how accurately the rates of $HFOs_{>80Hz}$, $HFOs_{>150Hz}$, and $HFOs_{>250Hz}$ predicted the seizure-onset sites. The next aim was to determine how accurately, but undesirably, the rates of these HFO rates detected the nonepileptic sensorimotor–visual sites clinically defined by neurostimulation. We subsequently measured $MI_{(HFOs)\&(3-4Hz)}$ and $MI_{(HFOs)\&(0.5-1Hz)}$ at all electrode sites, and determined how accurately the seizure-onset and nonepileptic sensorimotor–visual sites were detected by $MI_{(HFOs)\&(3-4Hz)}$ and $MI_{(HFOs)\&(0.5-1Hz)}$, respectively. According to the results of previous studies (Nagasawa et al., 2012; Wang et al., 2013), we expected that seizure-onset sites would be associated with increased $MI_{(HFOs)\&(3-4Hz)}$ and that nonepileptic sensorimotor–visual sites would be associated with increased $MI_{(HFOs)\&(0.5-1Hz)}$. Specifically, we tested the hypothesis that subtraction-MI_{HFOs} [defined as subtraction of $MI_{(HFOs)\&(0.5-1Hz)}$ from $MI_{(HFOs)\&(3-4Hz)}$] would localize the seizure-onset sites with reduced detection of the nonepileptic sensorimotor–visual sites.

2. Methods

2.1. Patients

The inclusion criteria consisted of: (i) a two-stage epilepsy surgery using extraoperative subdural ECoG recording in Children's Hospital of Michigan, Detroit, between October 2013 and September 2014, (ii) ECoG sampling from all four lobes of the affected hemisphere, and (iii) habitual seizures captured during extraoperative ECoG recording. The exclusion criteria consisted of (i) presence of massive brain malformations, such as large porencephaly, perisylvian polymicrogyria, or hemimegalencephaly, which are known to confound the anatomical landmarks for the central, calcarine, and sylvian sulci, (ii) undergoing hemispherectomy, and (iii) age of six years and younger (Haseeb et al., 2007). We studied a consecutive series of 13 children with a diagnosis of medically-uncontrolled focal epilepsy (age range: 7.9–18.8 years; 10 females; Table 1) who satisfied the inclusion and exclusion criteria. The study has been approved by the Institutional Review Board at Wayne State University, and written informed consent was obtained from the guardians of all patients.

2.2. Subdural electrode placement

Platinum macro-electrodes (inter-contact distance: 10 mm; contacts: 104–144 per patient) were placed in the subdural space generously over the affected hemisphere (Supplementary Figs. S1–S3), to satisfactorily determine the boundaries between the epileptogenic zone and eloquent areas (Nariai et al., 2011; Nagasawa et al., 2012). Our standardized placement of subdural electrodes included strip electrodes over the medial and inferior surfaces of temporal and occipital lobes, an 8-by-8 grid electrode array over the lateral temporal–frontal–parietal surface including the pre- and post-central gyri. Additional strip electrodes were placed on the inferior surface of the frontal lobe as well as the medial surface of the frontal–parietal region, based on the results of non-invasive presurgical evaluation using scalp video-EEG, MRI and glucose-metabolism positron emission tomography (PET). Such widespread cortical coverage has been commonly practiced,