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High frequency oscillations are less frequent but more specific to epileptogenicity during rapid eye movement sleep

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HIGHLIGHTS

- Occurrence of high frequency oscillations (HFOs) is generally suppressed during rapid eye movement sleep (REM) compared with slow wave sleep (SWS).
- Relatively frequent HFOs during REM were associated with area of surgical resection in patient with seizure freedom.
- Weaker suppressive effect of REM on HFOs may provide a specific marker of epileptogenicity.

ABSTRACT

Objective: We hypothesized that high frequency oscillations (HFOs) are differently suppressed during rapid eye movement sleep (REM) between epileptogenic and less epileptogenic cortices, and that the suppressive effect can serve as a specific marker of epileptogenicity.
Methods: Intracranial electroencephalography (EEG) was recorded in 13 patients with drug-resistant epilepsy. HFOs between 80 and 200 Hz were semi-automatically detected from total 15-min EEG epochs each for REM and slow wave sleep (SWS). z-Score of HFO occurrence rate was calculated from the baseline rate derived from non-epileptogenic cortex. Intracranial electrodes were labeled as REM dominant HFO (RdH) if REM z-score was greater than SWS z-score or as SWS dominant HFO (SdH) if SWS z-score was greater than REM z-score. Relationship of electrode location to the area of surgical resection was compared between RdH and SdH electrodes.
Results: Out of 1070 electrodes, 101 were defined as RdH electrodes and 115 as SdH electrodes. RdH electrodes were associated with the area of resection in patients with postoperative seizure freedom ($P < 0.001$), but not in patients without seizure freedom.
Conclusions: HFOs near the epileptogenic zone are less suppressed during REM.
Significance: The less suppressive effect of REM may provide a specific marker of epileptogenicity.

1. Introduction

High-frequency oscillations (HFOs) are electroencephalography (EEG) markers of epileptogenicity, and can be categorized into ripples (80–200 Hz) and fast ripples (>200 Hz) according to their frequency. Interictal HFOs are associated with the seizure onset zone (Staba et al., 2002; Jirsch et al., 2006; Urrestarazu et al., 2007; Jacobs et al., 2008, 2009; Bagshaw et al., 2009; Zijlmans et al., 2009; Crépon et al., 2010; Wang et al., 2013) and removal of the brain region hosting high rates of interictal HFOs is related to good seizure outcome after surgery (Jacobs et al., 2010; Akiyama et al., 2011; Zijlmans et al., 2012; Haegelen et al., 2013; Okanishi et al., 2014). In addition, a strong association is supported by the observed increases in occurrence of both HFOs and seizures following reduction of medication (Zijlmans et al., 2009).

Interictal HFOs are generated both by epileptogenicity and by physiological processes related to specific brain functions. Therefore, the diagnosis of epileptogenicity must distinguish

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pathological HFOs from physiological HFOs. For example, hippocampal ripples are important in memory consolidation (Girardeau and Zugaro, 2011). Memory processing is associated with HFOs distributed over the amygdala, hippocampus and specific neocortical areas in humans (Kucewicz et al., 2014). HFOs can be evoked by visual stimuli in the occipital cortex (Nagasawa et al., 2012) and by somatosensory stimuli in the somatosensory cortex (Hashimoto, 2000). Fast ripples are more strongly related to epileptogenicity than ripples (Bragin et al., 1999a,b; Staba et al., 2002, 2004; Engel et al., 2003). However, pathological HFOs are still difficult to differentiate from physiological HFOs.

The present study investigated the effect of sleep stages on epileptic activities as an indicator for the differentiation of epileptic from physiological HFOs. Previous studies showed that both spikes and HFOs appear less frequently in rapid eye movement sleep (REM) than in slow wave sleep (SWS). Interestingly, epileptic spikes are infrequent during REM, but the area of spikes is more specific to the primary epileptogenic areas (Lieb et al., 1980; Sammaritano et al., 1991) or hemispheres (Ochi et al., 2011). However, no studies have demonstrated such a difference in HFO distribution between REM and SWS (Bagshaw et al., 2009). Here we hypothesized that REM suppresses HFO occurrence, but has different effects in epileptogenic and less epileptogenic cortices, so that evaluation of the sleep-related HFO suppression would be useful in the diagnosis of epileptogenicity.

2. Methods

This study was approved by Tohoku University Institutional Review Board.

2.1. Patients

This study included 13 consecutive patients, 5 males and 8 females aged 12–41 years (mean age 25.4 years), with drug-resistant epilepsy who underwent extra-operative intracranial EEG monitoring for surgical treatment of epilepsy between May 2012 and January 2014 in the Tohoku University Hospital Comprehensive Epilepsy Program. All patients were qualified for intracranial electrode implantation after comprehensive pre-surgical evaluation and patient management conference. Consequently, 12 patients underwent resection surgery and one patient was excluded from surgical treatment. Six patients achieved seizure freedom at 1 year postoperative follow-up examination (Engel's classification class I). The clinical characteristics of the patients are summarized in Table 1. Preoperative epilepsy diagnosis included temporal lobe epilepsy in five patients, frontal lobe epilepsy in four, fronto-temporal lobe epilepsy in two, parietal lobe epilepsy in one, and occipital lobe epilepsy in one patient. Seven patients underwent surgery on the left. Brain magnetic resonance imaging (MRI) found no abnormalities in four patients.

2.2. Implantation of intracranial electrodes

Implantation of intracranial electrodes was designed to cover the probable epileptogenic area and, if necessary, to study the relationship between the epileptogenic area and functional cortex. Electrodes were implanted under general anesthesia, guided by a neuronavigation system (Brainlab®, Brainlab AG, Feldkirchen, Germany). Depth electrodes were inserted using a frameless stereotactic system (VarioGuide™, Brainlab AG).

Depth electrodes consisted of six cylindrical platinum contacts of 1.3-mm length and 1.1-mm diameter (Ad-Tech Medical Instrument Corporation, Racine, WI). All six contacts were aligned at 10-mm intervals in one type, and the first four contacts were aligned at 5-mm intervals, the next contact at a 15-mm interval, and the last contact at a 10-mm interval in the other type. All contacts were mounted on a 1.1-mm wide flexible plastic probe. Subdural or strip electrodes consisted of platinum discs with 3-mm diameter, embedded on a silicone sheet at inter-electrode distances of 10 mm (Ad-Tech Medical Instrument Corporation). The exposed area of the disc was 2.3 mm in diameter. A previous study showed that intracerebral electrodes with contacts between 0.2 and 5 mm^2 possessed similar HFO detection abilities (Châtillon et al., 2013). Depth and subdural electrodes were treated as having similar recording properties.

The location and number of electrodes are summarized in Table 2. Subdural electrodes were combined with depth electrodes in 11 patients. Two patients with temporal lobe epilepsy underwent bilateral electrode implantation. Medians of 18 depth electrodes (range 0–30) and 80 subdural electrodes (range 8–130) were used per patient. A total of 1192 contacts, including 198 depth and 994 subdural electrodes, were implanted across all patients. A total of 114 depth contacts were located in the hippocampus.

A total of 122 contacts (10.2%) were excluded as "bad electrodes" from later analysis, so the EEGs were obtained from the remaining 1070 contacts. The bad electrodes included 105 contacts clearly located in the white matter and 17 contacts with physically bad condition, such as disconnection. Disconnection was judged on raw signal waveforms as no visible EEG or contamination with high intensity noise.

2.3. Anatomical location of electrodes and surgical resection

Three-dimensional magnetization prepared rapid gradient echo (3D-MPRAGE) imaging and three-dimensional computed tomography (3D-CT) were performed before electrode implantation and on day 7 after implantation. These anatomical images were coregistered by linear affine transformation. The transformation was completed by maximization of mutual information by changing the coordinates and angles of the target images using Amira version 5 (Visualization Sciences Group, Inc., Burlington, MA). Locations of electrodes were visualized as metallic artifacts in the post-implantation CT scans coregistered on the preoperative 3D-MRIs. Postoperative 3D-MPRAGE imaging was coregistered to the preoperative 3D-MPRAGE image and CT scan. The area of surgical resection and the relationship to the electrode location were defined visually on the fusion image. Pre- and postoperative images were obtained with a 3-T MRI scanner (MAGNETOM Trio 3T, Siemens AG, Munich, Germany) and post-implantation images with a 1.5-T MRI scanner (Intera Achiva 1.5T NOVA DUAL, Royal Philips, Amsterdam, the Netherlands).

2.4. EEG recording

Intracranial EEG signals were sampled and recorded at 1000 Hz (Neurofax EEG-1200, Nihon-Kohden Co., Tokyo, Japan), simultaneously with scalp EEG and electromyography (EMG)/electro-oculography for sleep staging. Scalp electrodes were attached to 21 locations according to the international 10–20 system together with bilateral surface anterior temporal electrodes (Silverman, 1960). Two electrodes were attached to the mentalis muscle for EMG. Two electrodes were attached to the upper left to the left eye and to the lower right to the right eye, respectively, for electro-oculography.

2.5. EEG samples for HFO analysis

Video-EEG monitoring was performed for 14 days in 11 patients and for 21 and 26 days in the other two patients (Cases 2 and 13).

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