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Epileptogenic high-frequency oscillations skip the motor area in children with multilobar drug-resistant epilepsy

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HIGHLIGHTS

- Occurrence rate of high-frequency oscillations [$OR_{(HFO)}$] and modulation index [$MI_{(3–4\ Hz)}$] were significantly higher in resection areas in the good (vs. poor) outcome group.
- The $OR_{(HFO)}$ and $MI_{(3–4\ Hz)}$ skipped the motor area in children requiring subtotal hemispherectomy.
- The $OR_{(HFO)}$ and $MI_{(3–4\ Hz)}$ could be valuable biomarkers to identify epileptogenic extra-motor areas.

ABSTRACT

Objective: Subtotal hemispherectomy involves the resection of multiple lobes in children with drug-resistant epilepsy, skipping the motor area (MA). We determined epileptogenicity using the occurrence rate (OR) of high-frequency oscillations (HFOs) and the modulation index (MI), demonstrating strength of coupling between HFO and slow wave. We hypothesized that epileptogenicity increased over the multiple lobes but skipped the MA.
Methods: We analyzed 23 children (14 subtotal hemispherectomy; 9 multilobar resections). Scalp video-EEG and magnetoencephalography were performed before surgery. We analyzed the $OR_{(HFO)}$ and $MI_{(5\ phases=0.5–8\ Hz)}$ on electrodes of total area, resection areas, and MA. We compared the data between good [International League Against Epilepsy (ILAE) class I–II] and poor (III–VI) seizure outcome groups.
Results: ILAE class Ia outcome was achieved in 18 children. Among the $MI_{(5\ phases)}$ in the resection areas, $MI_{(3–4\ Hz)}$ was the highest. The $OR_{(HFO)}$ and $MI_{(3–4\ Hz)}$ in both total area and resection areas were significantly higher in the good seizure outcome group than in the poor outcome group. The $OR_{(HFO)}$ and $MI_{(3–4\ Hz)}$ in resection areas were significantly higher than in the MA.
Conclusions: Our patients with multilobar drug-resistant epilepsy showed evidence of multifocal epileptogenicity that specifically skipped the MA.
Significance: This is the first study demonstrating that the electrophysiological phenotype of multifocal epilepsy specifically skips the MA using $OR_{(HFO)}$ and $MI_{(3–4\ Hz)}$.

Abbreviations: MA, motor area; IVEEG, intracranial video electroencephalography; HFO, high-frequency oscillation; FR, fast ripples; OR, occurrence rate; MI, modulation index; F, frontal area; T, temporal area; PO, parieto-occipital area; SVEEG, scalp video electroencephalography; MRI, magnetic resonance imaging; MEG, magnetoencephalography; ILAE, International League Against Epilepsy; NREM, non-rapid eye movement; PET, Positron emission tomography; FCD, focal cortical dysplasia; TSC, tuberous sclerosis complex; CCEP, cortico-cortical evoked potentials.

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1. Introduction

1.1. Subtotal hemispherectomy

Multilobar resections for drug-resistant epilepsy are much more common in pediatric than in adult patients (Leiphart et al., 2001). In children requiring multilobar resections, seizure-free outcome varied from 22% to 92% (Eriksson et al., 1999; Paolicchi et al., 2000; Chugani et al., 2014; Nilsson et al., 2016). "Subtotal hemispherectomy" is a form of multilobar resection where the whole cerebral cortex of one hemisphere is resected, except for the primary sensorimotor cortex (Chugani et al., 2014). In our epilepsy surgery population of children at the Hospital for Sick Children, involving children with drug-resistant multilobar epilepsy, we have often observed during intracranial video electroencephalography (IVEEG) that the multiple epileptic foci often skip the motor area. These observations have led to the current work in which we quantitatively delineated differences of the epileptogenicity between the multilobar resection areas and the motor area.

1.2. HFO

A number of studies have described both pathological and physiological high-frequency oscillations (HFOs) (Buzsáki et al., 1992; Matsumoto et al., 2013). Physiological HFOs are considered to play an important role in vision, motor, language, and memory functions (Gray and Singer, 1989; Buzsáki et al., 1992; Crone et al., 2011). Pathological HFOs consist of ripples (80–200 Hz) and fast ripples (FRs) (>200/250 Hz), which are specific biomarkers of epileptogenicity (Jacobs et al., 2010; Wu et al., 2010; Akiyama et al., 2011). The removal of pathological HFOs has been reported to result in excellent postsurgical seizure outcomes. (Bragin et al., 1999; Engel et al., 2009; Bragin et al., 2010; Worrell and Gotman, 2011; Matsumoto et al., 2013; Höller et al., 2015; von Ellenrieder et al., 2016). Akiyama et al. reported that interictal high-rate FRs are a potential marker of the epileptogenicity (Akiyama et al., 2011). Okanishi et al. reported that resection of multiple areas with interictal high-occurrence rate (OR) HFOs is associated with better post-surgical seizure outcome in children with tuberous sclerosis (Okanishi et al., 2014). The present study is the first analysis of HFOs in children with drug-resistant epilepsy who underwent subtotal hemispherectomy and multilobar resections sparing the motor area.

1.3. Modulation index

Phase-amplitude coupling, compared to the rate of HFOs, has been suggested to be more useful for the localization of an epileptic focus (Weiss et al., 2013). Modulation index (MI) measures the strength of phase-amplitude coupling between the amplitude of HFO and the phase of slow wave (Canolty et al., 2006). By measuring MI at the seizure onset zone and stimulation-defined eloquent areas, Nonoda et al. (2016) suggested that pathological HFO may be coupled with slow waves at 3–4 Hz more preferentially than at 0.5–1 Hz, whereas physiological HFO is coupled with slow wave at 0.5–1 Hz more preferentially than at 3–4 Hz during slow-wave sleep. The current study delineates the characteristics of MI in children who required subtotal hemispherectomy and multilobar resections with sparing of the motor area.

1.4. Hypothesis

Our objectives were to determine the distribution of pathological HFOs in children with drug-resistant epilepsy who underwent subtotal hemispherectomy and multilobar resections. We analyzed the $OR_{(Ripple/FR)}$ and $MI_{(Ripple/FR\ \&\ 5\text{-phase slow waves})}$ on the intracranial electrodes in the total area, resection areas, and motor area.

We tested the hypotheses that (1) pathological HFOs are distributed over multilobar epileptogenic zones in children who underwent subtotal hemispherectomy and multilobar resections for drug-resistant epilepsy and (2) the epileptogenic HFOs skip the motor area in these children.

2. Methods

2.1. Patients

From June 2009 to December 2013, 24 children with drug-resistant multilobar onset drug-resistant epilepsy underwent IVEEG prior to epilepsy surgery at the Hospital for Sick Children. We excluded 1 child in whom the motor area was not detected. We analyzed the data from the remaining 23 children. We performed scalp video-EEG (SVEEG), magnetic resonance imaging (MRI), and magnetoencephalography (MEG) before IVEEG. This study was approved by the Research Ethic Board at the Hospital for Sick Children.

2.2. IVEEG recording

We decided the hemisphere to implant the subdural grid electrodes by considering the seizure semiology, ictal/interictal findings on SVEEG, MRI lesions, and MEG spike dipoles. We implanted several strip and/or depth electrodes for the lesions in addition to the subdural grid electrodes if the lesion or the presumed epileptogenic zone required this procedure (Fig. 1). Our procedure of intracranial electrode placement has been previously reported (Ochi et al., 2007; Akiyama et al., 2011; Okanishi et al., 2014). The subdural electrodes (diameter: 4 mm; exposure: 2.3 mm; effective surface area: 4.2 mm^2; intercentral distance: 9–13 mm) and the depth electrodes (surface area: 8.3 mm^2; intercentral distance: 7 mm) were implanted (Ad-Tech Medical Instrument, Racine, WI, U.S.A.). IVEEG data were acquired by using HARMONY 5.4 (Stellate, Montreal, PQ, Canada). Our sampling rate was 1 kHz with the anti-aliasing filter at 300 Hz or 2 kHz with the

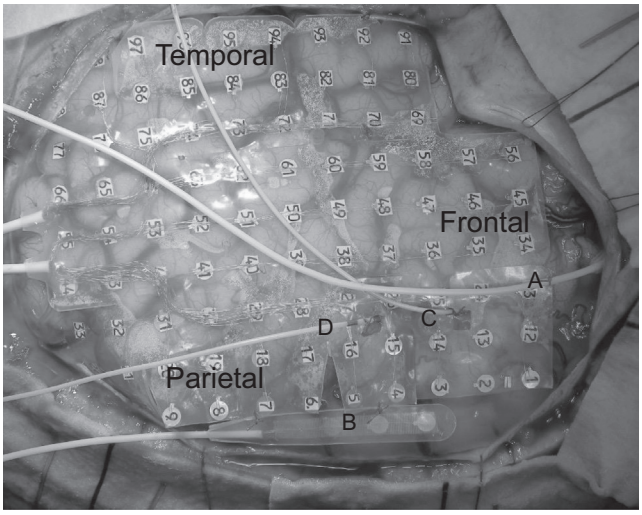

Fig. 1. Intracranial electrode placement. Total 109 electrodes are implanted, consisting of 93 subdural grid electrodes over the left fronto-parieto-temporal region. Two 4-contact strip electrodes are placed over the left frontal pole (A) and the left superior frontal gyrus (B). Two 4-contact depth electrodes are inserted over the left superior frontal gyrus (C and D) (Patient #10).