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Prediction of seizure outcome improved by fast ripples detected in low-noise intraoperative corticogram

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HIGHLIGHTS

- Low-noise EEG increases the signal-to-noise ratio in the fast ripple frequency band.
- Unsupervised fast ripples detection standardizes the definition of clinically relevant fast ripple.
- Prediction of seizure outcome was improved by the optimal integration of the low-noise EEG and the unsupervised fast ripples detection.

ABSTRACT

Objective: Fast ripples (FR, 250–500 Hz) in the intraoperative corticogram have recently been proposed as specific predictors of surgical outcome in epilepsy patients. However, online FR detection is restricted by their low signal-to-noise ratio. Here we propose the integration of low-noise EEG with unsupervised FR detection.
Methods: Pre- and post-resection ECoG ($N = 9$ patients) was simultaneously recorded by a commercial device (CD) and by a custom-made low-noise amplifier (LNA). FR were analyzed by an automated detector previously validated on visual markings in a different dataset.
Results: Across all recordings, in the FR band the background noise was lower in LNA than in CD ($p < 0.001$). FR rates were higher in LNA than CD recordings (0.9 ± 1.4 vs 0.4 ± 0.9, $p < 0.001$). Comparison between FR rates in post-resection ECoG and surgery outcome resulted in positive predictive value PPV = 100% in CD and LNA, and negative predictive value NPV = 38% in CD and NPV = 50% for LNA. Prediction accuracy was 44% for CD and 67% for LNA.
Conclusions: Prediction of seizure outcome was improved by the optimal integration of low-noise EEG and unsupervised FR detection.
Significance: Accurate, automated and fast FR rating is essential for consideration of FR in the intraoperative setting.

1. Introduction

Interictal High Frequency Oscillations (HFOs) recorded in epileptic brain tissue have been identified as a reliable biomarker for the delineation of the epileptogenic zone (Jacobs et al., 2012; Zijlmans et al., 2012b). HFOs are classified according to their spectral range in ripples (80–250 Hz) and fast ripples (FR, 250–500 Hz) (Bragin et al., 2010). Intraoperative ECoG studies have specifically

Abbreviations: ADC, analog-to-digital conversion; CD, commercial device; CI, confidence interval; FCD, focal cortical dysplasia; FR, fast ripple; FRandRip, FR occurring together with ripple; HFO, high frequency oscillation; ILAE, International League Against Epilepsy; LNA, low-noise amplifier; LSD, linear spectral density; MTS, mesial temporal sclerosis; NPV, negative predictive value; ODG, oligodendroglioma; PPV, positive predictive value; SNR, signal-to-noise ratio.

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pointed at FR as reliable predictors of seizure outcome in epilepsy surgery (Wu et al., 2010; van't Klooster et al., 2015).

FR are very localized events with low signal-to-noise ratio (SNR) that may fail to stand out from the background noise of ECoG recordings. Peak-to-peak amplitude values amount to a few tens of μV for ripples and a few μV for FR (Bragin et al., 2010; Zijlmans et al., 2012b). SNR is affected by physiological background activity, anaesthesia (Zijlmans et al., 2012b) and recording system noise, particularly in the FR spectral range (Scheer et al., 2006, 2011; Fedele, 2014). Recent technological advances over commercial devices (CD) led to the development of a dedicated low-noise amplifier (LNA), facilitating the detection of high frequency somatosensory features in the FR spectral range with single trial resolution in scalp recordings (Waterstraat et al., 2015a,b) and up to 1 kHz for the averaged evoked response (Fedele et al., 2012, 2015).

While HFO analysis in ECoG is usually performed by visual or supervised automated procedures that are time consuming and prone to bias, we have significantly improved automated detection (Burnos et al., 2014; Fedele et al., 2016).

We here evaluate the clinical benefit of FR detected in low-noise ECoG. We simultaneously recorded ECoG with a CD and a custom-made LNA, applied fully automated HFO detection, and quantified the predictive power of HFO rates with respect to seizure outcome.

2. Methods

2.1. Patients and ECoG recordings

We included nine patients (6 females; median age 6 years, range [3–67], Table 1) that underwent resective epilepsy surgery using intraoperative ECoG to delineate the epileptogenic zone at the Department of Neurosurgery of the University Hospital in Zurich from August to December 2015. We collected 22 ECoG (129 bipolar channels, median duration 3 min [range 1.1–6], mean duration 4.1 ± 2.1 min). Postsurgical seizure outcome was classified according to the ILAE (Wieser et al., 2001), dichotomized into seizure freedom (ILAE 1) and seizure recurrence (ILAE 2–6) outcome. Follow-up was >12 months after surgery. The collection of patient data and their retrospective analysis was approved by the institutional ethics review board (Kantonale Ethikkommission KEK ZH-Nr. 2012–0212) and the collection of patients' written informed consent was waived. The study was registered internationally at clinicaltrials.gov (NCT02320136).

2.2. Anaesthesia management

Following our standard protocol for neurosurgical interventions, anaesthesia was induced with intravenous application of Propofol (1.5–2 mg/kg) and Fentanyl (2–3 μg/kg). Intratracheal intubation was facilitated by Atracurium (0.5 mg/kg). Anaesthesia was maintained with Propofol (5–10 mg/kg/h) and Remifentanil (0.1–2 μg/kg/min). Twenty minutes before ECoG recording, Propofol was ceased and anaesthesia was sustained with sevoflurane (MAC < 0.5).

2.3. Recording setup

Subdural strip or grid electrodes (1 × 4, 1 × 6 and 2 × 4 contacts, contact diameter 6 mm with a 5 mm exposure, spacing between contact centres 10 mm, Ad-Tech Medical, Racine, WI, USA) were placed directly on the cortex after craniotomy for ECoG. We connected active lead, reference lead and ground lead of the electrodes in parallel to the active lead, reference lead and ground lead of the CD and LNA. The CD, featuring an input noise level of ~21 nV/√Hz, was either the ISIS® IONM (Intraoperative neural monitoring, 16 bit analog-to-digital conversion (ADC), Inomed Medizintechnik GmbH, Emmendingen, Germany; sampling rate 10 kHz, 5–2500 Hz bandpass, input range ±5 mV, LSB 0.153 μV) in 3 cases, or the Nicolet® CSeries amplifier (Natus Medical Incorporated, 16 bit ADC, Pleasanton, PA, USA; sampling rate 2 kHz, 1–800 Hz bandpass, input range ±5 mV, LSB 0.153 μV) in the other 6 cases. The custom-built LNA featured an input noise level of 2.3 nV/√Hz, (24 bit ADC, 10 kHz sampling rate, 0.1–3000 Hz bandpass, input range ±5 V combined with gain 100, LSB = 6 nV) (Scheer, 2013; Fedele, 2014; Fedele et al., 2015; Waterstraat et al., 2016). The LNA is battery powered, which prevents interference with the CD system. Details on the design of the amplifier are covered by a patent (Scheer, 2013). The advantage of the LNA in the high frequency range is described in Supplementary Material S2. Impedances were typically below 2 kΩ. Where necessary, data were downsampled to 2 kHz for further processing (Matlab® function "resample"). The ECoG was analyzed after bipolar re-referencing along consecutive strip and grid contacts, obtaining the same re-referenced signal for CD and LNA. We specifically tested for mismatch in ADC timing and gain across channels and found no evidence for their contribution to noise in the HFO frequency range.

Table 1
Pre- and post-resection HFO rates and postsurgical outcome. For each patient, ripple and FR rate in pre- and post-resection ECoG are reported for CD and LNA recordings. Rates are expressed as averages across all channels with events for each patient. PPV and NPV were computed for the post-resection ECoG rates. ODG = oligodendroglioma; FCD = focal cortical dysplasia; MTS = mesial temporal sclerosis; F = frontal; T = temporal; P = parietal; O = occipital; L = left; R = right; PPV = positive predictive value; NPV = negative predictive value; CD = commercial device; LNA = low- noise amplifier.

Patient	Age, gender	Pathology	Location	Ripple rates [1/min]				FR rates [1/min]				Seizure outcome (ILAE)	Months after surgery
				Pre-resection		Post-resection		Pre-resection		Post-resection			
				CD	LNA	CD	LNA	CD	LNA	CD	LNA		
1	17, m	FCD	LTO	n.a.	n.a.	4.2	6.5	n.a.	n.a.	–	–	>1	17
2	67, f	ODG (WHO II)	RPO	7.9	7.6	2	12.3	–	–	–	–	1	16
3	3, f	FCD	RT	1.5	3.9	–	–	–	1.5	–	–	1	16
4	4, m	FCD	LT	14.8	19	12.1	10.1	2.0	2.3	1.5	2.6	>1	15
5	17, m	MTS	RMT	1.6	1.2	1.4	1.2	–	–	–	–	>1	14
6	4, m	FCD	RT	11.9	9.1	3.6	3.3	7.0	3.3	–	2.8	>1	13
7	41, m	Cavernoma	RP	1.5	2.1	–	–	–	1.9	–	2.0	>1	13
8	6, f	FCD	LF	22.9	80.3	9.3	45.7	2	4.5	–	–	>1	13
9	5, f	FCD	RP	8.2	8.8	23.8	52	–	1.1	–	–	1	13
PPV						71%	71%			100%	100%		
NPV						50%	50%			38%	50%		
Accuracy						67%	67%			44%	67%		